"NEOADJUVANT SHORT COURSE RADIOTHERPY FOLLOWED BY SURGERY IN LOCALLY ADVANCED RECTAL CANCERS"

A SINGLE ARM PROSPECTIVE STUDY

Institution

DEPARTMENT OF RADIOTHERAPY
MADRAS MEDICAL COLLEGE
RAJIV GANDHI GOVERNMENT GENERAL HOSPITAL
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CERTIFICATE

This is to certify that **DR MADHULIKA VIJAYAKUMAR** has been a M.D postgraduate student during the period May 2012 to March 2016 in the Department of Radiotherapy, Madras Medical College, Government General Hospital, Chennai.

This Dissertation titled "**NEOADJUVANT SHORT COURSE RADIOTHERPY FOLLOWED BY SURGERY IN LOCALLY ADVANCED RECTAL CANCERS"** is a bonafide work done by her during her study period and is being submitted to the Tamil Nadu Dr.M.G.R Medical University in partial fulfillment of the M.D Branch IX Radiotherapy Examination.

PROF . DR. VIMALA,M.D.,
DEAN,
Madras Medical College &
Rajiv Gandhi Government General
Hospital,
Chennai.

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Prof. Dr.S. Shanmugakumar, B.Sc., M.D., DMRT,

Professor and Head,

Department of Radiotherapy,

Madras Medical College &

Rajiv Gandhi Government General Hospital,

Chennai.

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Dr. P. K. BASKAR, M.D.R.T

Dr. S. MADHUMATHI, M.D.R.T

Dr. SUNDARESAN, M.D.R.T

Dr. ARUN RAMANAN, M.D.R.T

Dr. PRABHAHARAN, DMRT

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DECLARATION

I solemnly declare that the dissertation titled "**NEOADJUVANT SHORT COURSE RADIOTHERPY FOLLOWED BY SURGERY IN LOCALLY ADVANCED RECTAL CANCERS"** STUDY was done by me at the Department of Radiotherapy, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai during **October2014 to August2015** under the guidance and supervision of Prof. Dr. S.SHANMUGAKUMAR.

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Dr. MADHULIKA VIJAYAKUMAR,

M.D. Radiotherapy,

Post Graduate Student,

Department of Radiotherapy.

Madras Medical College.

Place: Chennai

Date:

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INTRODUCTION:

Globally among various diseases, cancer has become a major threat to human beings. It has now become a disease which has perplexed many, doctors and patients alike is now one of the leading causes of death worldwide .As per Indian population census data, cancer related mortality rates are high and alarming. In India, cancer has become the most common disease, ranking second. It has become responsible for high mortality rates, with about 0.3 million deaths per year. This is mainly because of availability of resources is poor in a country ours. The resources are limited not only for prevention, screening, but also for diagnosis and treatment.

The cancer burden continues to increase globally, largely because of the aging of the population and also due to growth of the young population alongside with increase in adoption of cancer-causing behaviours, especially in economically developing countries. In our country the increase in cancer burden is mainly attributed to urbanisation, industrialisation, changes in life style , increase in population and increase in life span. The life expectancy has risen from 45 years in 1970's to 62 years in 1990's and 71 years is expected by 2021. Many

cancers are found to have some relation with the diet habits, one among them are cancers of gastrointestinal tract.

IMPACT OF CANCER IN INDIA:

Impact of cancer is much greater in India, than the mere number of cases of cancer. The very beginning of diagnosis of cancer causes immense emotional trauma to the patients and to their families, and its treatment a major economic burden. The diagnosis of cancer itself is perceived by most of them as a grave event, a curse with more than one-third of them suffering from some form of mood disorders (anxiety and depression). The family members also feel equally distressed. It could affect both family's daily functioning and economic situation. The economic blow often includes both loss of income and increase of expenses because of treatment and health care. In a country like India this disease is associated with a lot of fear & despair.

CANCER MANAGEMENT A CHALLENGE IN INDIA:

According to a study conducted by Boston Consulting Group , 70% cancer cases in India are diagnosed at advanced stages and, most of the patients do not have access to tertiary care centres. There are not many

cancer centers in India to meet the demand of treatment burden. More radiotherapy centers with adequate number of machines are required to cover cancer population adequately. Moreover, not all centers are well equipped with modern facilities. The current Doctor patient ratio is only 1 in 2000 and aim is to achieve, atleast 1 in 1000 by the year 2021.There is also disproportionate skillful manpower and technology with very few cancer specialists, trained staff available. And if present, these specialized cancer centers are available only in very few cities across India. For most patients in India, treatment cost is so heavy and out of reach. Neither people do not have insurance cover.Thus delivery of equitable, quality and affordable cancer care in India is a big challenge.

INCIDENCE OF COLORECTAL CANCERS:

The specialised cancer wing of the world health organisation, International Agency for Research on Cancer (IARC), released the latest data on cancer incidence, mortality, and prevalence worldwide in December 2013.[1] Their online database GLOBOCAN 2012, revealed the most recent estimates of incidence and prevalence rates of different cancers. Colorectal cancer has become the third most common cancer worldwide, with nearly 1.4 million new cases diagnosed in the year 2012. Of these ,majority of patients were men constituting about 7.4

million cases and women 6.7 million. This number is expected to rise to 2.4 million cases worldwide by 2035.It is predicted that worldwide, by the year 2035, the number of colorectal cases will increase to 1.36 million for men and for women 1.08 million. [(2)]

Amomg both sexes

- Lung cancer was the most common cancer worldwide constituting 13% of new cases diagnosed in 2012.
- Breast cancer (women only) was the second most common cancer with nearly 1.7 million new cases in 2012.
- **Colorectal cancer was the third most common cancer with nearly 1.4 million new cases in 2012.**

GEOGRAPHIC VARIATIONS:

The incidence of colorectal cancers is not uniform throughout the world. There is a large geographic variation in the global distribution.colorectal cancer. Colorectal cancer is mainly a disease of western developed countries with a with ten fold variation between countries with the highest rates than those with the lowest rates. It ranges from more than 40 per 100,000 people in the United

States, Australia, New Zealand, and Western Europe to less than 5 per 100,000 in Africa and some parts of Asia.(3)

MORTALITY RATES AND TRENDS:

Worldwide mortality due to colorectal cancer is approximately half of its incidence. Nearly about 530,000 deaths were recorded in the year 2012 , and it contributed to 8% of all cancer related deaths. In the United States,both in men and women , it has become the second leading cause of death among other cancers. The incidence rates are appropriate indicator of trends in disease occurrence. Colorectal cancer incidence is unaffected by changes in treatment and survival, although it has been shown to be influenced by improved diagnostic techniques and screening programs.(4)

CANCER SURVIVAL AND PROGNOSIS:

Survival is highly dependent upon stage of disease at the time of diagnosis, and 5-year survival rate ranges from 90% for cancers detected at the localized stage to 70% for regional and to 10% for patients diagnosed with distant metastasis. With recent improvements in

treatment strategies survival for all stages of colorectal cancer at has increased significantly. The better improvement in 5-year survival is seen in countries with high life-expectancy and good access to modern specialized treatment centers. Even then ,large disparities exist in colorectal cancer survival worldwide and even within same regions. (4)

RISK FACTORS:

There are many number of risk factors associated with increased incidence of colorectal cancer. Non modifiable risk factors are the ones that one cannot control, it includes age and inhereted factors. In addition to this, other factors in environment and lifestyle habits play a significant role in the development of colorectal cancer.

1. Age:

The likelihood of developing colorectal cancer increases as age increases above 40 .It sharply rises after 50 years of age. More than 90% of colorectal cancer cases occur in people aged 50 years or older. However, it seems to be increasing among younger population too, mainly because of western life style and dietary habits .

2. Personal History of Adenomatous Polyps:

Almost 95% of colorectal cancers due to sporadic causes develop from adenomatous polyps. Neoplastic polyps namely tubular and villous

Adenomas serve as the are precursor lesions for developing cancer . An person with a history of adenomatous polyps has an higher risk of developing colorectal cancer, than individuals with no such history of adenomas. A long latency period of about 5 to 10 years is required for transformation from ademomas to invasive lesions. Screening , early detection of these adenomatous polyps with subsequent removal before malignant transformation may reduce the risk of colorectal cancer. However, there always remains an increased risk of further development of metachronous cancers anywhere in the colon or rectum.

3. Personal History of Inflammatory Bowel Disease:

Inflammatory bowel disease (IBD) includes two main diseases, Crohn disease and ulcerative colitis. Crohn disease can involve any part of the gastro intestinal tract and it causes inflammation of the full thickness of the bowel wall. . Ulcerative colitis usually involves only colon and rectum. And it causes only mucosal inflammation. Both these inflammatory diseases increase the overall risk of developing colorectal cancer. The relative risk of patients with inflammatory bowel disease to develop colorectal cancers is estimated between 4- to 20-fold. Therefore,

individuals with inflammatory bowel diseases regardless of age are encouraged to undergo screening for colorectal cancer more frequently than the general population.

4. Family History of Colorectal Cancer or Adenomatous Polyps :

In about 20% of people who develop colorectal cancer have positive family history . It is higher in people with affected first degree relative younger than 60 years of age , or a history of colorectal cancer or adenomatous polyps in two or more first-degree relatives at any age. The increased risk is attributed to inherited genes, shared environmental factors, or combination of these factors.

5. Inherited Genetic Risk:

Nearly 5 to 10% of colorectal cancers are have recognisable hereditary factors. The most common among the inherited conditions include familial adenomatous polyposis (FAP) and ,Lynch syndrome also known as hereditary nonpolyposis colorectal cancer (HNPCC). Genes causing these forms of inherited colorectal cancer have been identified. HNPCC is associated with mutations in genes

the *MLH1* and *MSH2* , which are involved in the repair pathway DNAs. FAP is caused by mutations in APC genes ,which is a tumor suppressor gene . Lynch syndrome accounts for only 6 % of colorectal cancers, and individuals have a lifetime risk of developing cancer is as high as 70 to 80%.The average age at diagnosis is also younger , around 40 years. Patients with genetic mutations in genes involved in DNA mismatch repair , are also at a higher risk of developing many other cancers, namely cancer of the genitourinary tract, stomach, small bowel and pancreas. **FAP** accounts for only very few cases less than 1%. Unlike people with HNPCC, who develop only a few adenomas, individuals with FAP characteristically develop hundreds of polyps, at a relatively younger age, and one or more of these adenomatous polyps typically undergoes malignant transformation at a very early . All individuals with FAP, will developed cancer before the age of 40 if the colon is not removed prophylactically. *APC*-gene is inherited in an autosomal dominant fashion. Nearly 80% of people with *APC*-associated polyposis have atleast one affected parent. Prenatal testing and preimplantation genetic testing should be done , if the mutation is identified in any one of the parent.

6. Environmental Risk Factors :

Colorectal cancer develops due to various environmental factors, which includes cultural, social, and lifestyle modification . Colorectal cancer has many modifiable causes identified, and a significant proportion of cases may be theoretically preventable. Some of the evidence of environmental risk factors as causes comes from studies of migrants and their offspring. Between migrants from low-risk to high-risk countries, incidence rates tends to increase toward those of the populationbelonging to the host country. The incidence of colorectal cancer in the offspring of migrants from Japan to United States, equal to or it may surpasses that in naïve American population. This is three or four times higher than among the Japanese in Japan. Not only migration, there are other geographic factors influencing incidence rates too. One among them is living in urban residence. The incident rates are constantly found to be higher among urban residents. This excess incidence in urban areas is more apparently seen in males than females , and more so for colon cancer than rectal cancer.

7. Dietary habits:

Diet strongly influences the risk of colorectal cancer . Several studies have shown that changes in food habits may reduce to 70% of this cancer incidence . Diets rich in fat, especially fats of animal origin has shown to be a major risk. The association of animal fat, as a possible etiologic factor, is linked to the concept of the Westernization of diet habits, which favors the growth of gut bacterial flora. These are capable of degrading the bile salts to potentially carcinogenic *N*-nitroso compounds. Consumption of high meat has also shown to an risk factor in the development of colorectal cancer. This positive association of cancer with meat consumption is more so for colon cancer than rectal cancer. It is mainly because of presence ofm heme iron in red meat. In addition to this ,some meats products are cooked at very high temperatures, resulting in the production of heterocyclic amines and polycyclic aromatic hydrocarbons. Both of these compounds are believed to be carcinogenic .

Some studies have shown that individuals whose food habits includes less fruits and vegetables , have a relatively higher risk of cancer. Differences in dietary fiber consumption might be responsible for the geographic variation in the incidence rates. The basic mechanism is that increased

intake of dietary fiber may cause dilution of fecal content thereby increasing the fecal bulk, and reducing the bowel transit time.

8. Physical Activity and Obesity :

Several habits related to lifestyle modification has been linked to increase the risk of colorectal cancer. Two modifiable risk factors ,which are also interrelated to each other , are physical inactivity and excess body weight. These two factors account for about one fourth to one third of colorectal cancers. There is also abundant data to support , that higher levels of physical activity are associated with lowered risk of cancer. Studies have shown that dose–response effect exist, with frequency and intensity of physical activity inversely associated with risk of developing cancer. Regular physical activity and a healthy dietary habits can help individuals to decrease the risk, although the evidence is much higher for colon cancers than for rectal cancers. The biologic mechanisms potentially responsible for the association is that, physical activity raises the BMR and increases oxygen uptake by the cells. In the long run, regular periods of physical activity increase the individuals metabolic efficiency and capacity, it as well as reduces the blood pressure and, prevents development of insulin resistance. In addition, physical activity

also increases gut motility. Physical inactivity in daily routines attributes to the increased incidence of boby mass index in both males and females, another risk factor associated with increased incidence.

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ROLE OF VITAMIN D IN COLORECTAL CANCERS:

Prospective studies has shown that lower levels of vitamin D is associated with significant increase in mortality among patients with colorectal cancers. In systemic review and meta-analysis of around 2000 patients with colorectal cancers, compared patients with high level and low levels of vitamin D. It was found that OS and disease specific mortality aes were better for patients with higher levels . Yet , no specific data exist to prove that vitamin D supplementation improves patient outcomes.

HISTOLOGICAL CLASSIFICATION:

More than 90% of colorectal cancers are adenocarcinomas.

Other histological subtypes include

- Adenocarcinoma *in situ*

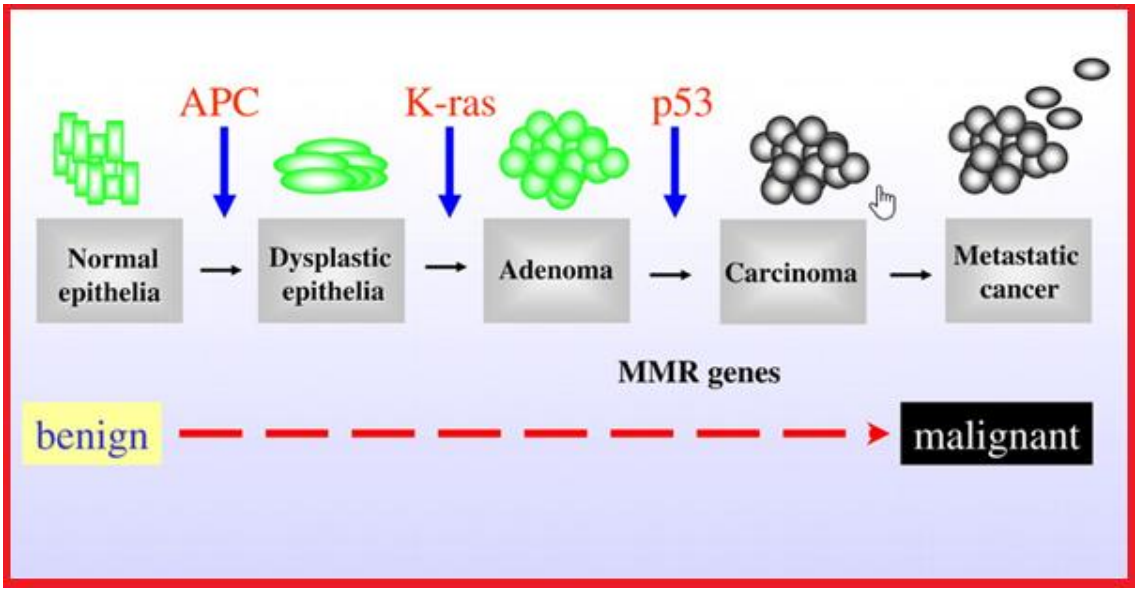
- Medullary carcinoma
- Mucinous carcinoma (colloid type) (greater than 50% mucinous carcinoma)
- Signet ring cell carcinoma (greater than 50% signet ring cell)
- Adenosquamous carcinoma
- Small cell carcinoma
- Undifferentiated carcinoma
- Carcinoma, NOS
- Squamous cell (epidermoid) carcinoma

PATHWAYS OF SPREAD:

- Lymphatic channels and lymph nodes.
- To liver and lung by hematogenous spread .
- It also has propensity to spread within the bowel wall mainly longitudinally.

PATHOGENESIS:

Figure 5: PATHOGENESIS



PROGNOSTIC FACTORS INFLUENCING SURVIVAL:

- depth of tumor invasion - T stage of the tumor.
- The number of regional lymph nodes involved.
- Vascular or lymphatic channel invasion.

- Presence of residual tumor following surgery- it relates to positive surgical margins.
- Grade of the tumor.
- Status of Radial margin .
- Following Neo adjuvant chemo radiation – presence of residual tumor.
- Histology, and association with microsatellite instability (MSI).

RATIONALE FOR THE PRESENT STUDY:

As seen already, colorectal cancers are very common in our country. In our institution too they constitute 10% to 15% of the cancers registered in the OPD. And most of them present in the locally advanced stages. The presently available standards of the treatment with surgery and concurrent chemo radiation have a dismal performance in long term control with overall survival at 2 years hovering around the 50% mark and less than 20% surviving 5 years. Various modalities are being devised to overcome this.

This is where the intensification of the treatment is considered. The long course neo adjuvant chemo radiation has its own toxicity profile, leading to treatment breaks and decreased compliance. The argument for neo adjuvant radiation before the loco regional treatment is that it results in reduction of the tumor load, thereby resulting in better loco regional control. Also it has been alleged that adjuvant radiation has increased risk of small bowel toxicity and also decreased responsiveness because the blood supply to the local areas would have been altered. When the same is given in the neo adjuvant setting, the blood circulation in these areas is intact and will supposedly result in better results.

With these understandings, there has been a renewed interest in addressing locally advanced rectal cancers with neo adjuvant radiation in the form of short course for selected patients. So the present study justified in addressing this question.

LITERATURE REVIEW:

Before 1900, incidence of colon and rectal cancers were negligible. Since then , following economic development and industrialization the incidence has been rising dramatically. For all rectal cancers, surgery remains as the primary treatment modality .Despite these curative resection, local recurrence remains high. Anatomical confines of pelvis and the importance of preservation of autonomic nervous system makes surgery very challenging. This may account for high rates of both local recurrence and distal relapse.

Many European randomized prospective trials have shown that multimodality approach results in significant better outcome. Neo adjuvant treatment has emerged as the standard of care and degree of tumor regression has become an important prognostic factor. A multi modality approach including medical oncology , radiation oncology and colorectal surgery is required for optimal treatment plan.

Multiple randomized trials have shown that addition of preoperative chemo radiation has shown significant benefit, resulting in increased pathological response rates and increased local control rates. Earlier in 1900's ,the National Institute of Health consensus

recommended combined treatment modality for stage II and III rectal cancer, based on observation from Gastrointestinal tumor study group and National surgical adjuvant breast and bowel project trials, which demonstrated chemotherapy along with radiation, following surgical resection reduces the rates of local recurrence to 33% from 55%.It has also shown to prolong the disease-free survival rates .

ADVANTAGES OF PREOP CHEMORADIATION:

1. Downsizing the tumor volume, facilitates resection and increase the likelihood of sphincter saving procedures.

2. Irradiating the tissues before surgery, which has better oxygenation than the postop tumor bed tissues, and may result in increased responsiveness to RT.

3. Avoidance of radiotherapy induced injury to small bowels, which has dropped down into the pelvis by post surgically.

4. The irradiated structures will be removed by surgery, anastamosis is with healthy Colon.

DISADVANTAGES OF POST OP RT :

1. Hypoxic post surgical bed makes radiation & chemotherapy less effective.

2. Increased small bowels in the radiation field,is a dose limiting organ, and it increases chances of both acute and late toxicity.

SWEDISH RECTAL TRIAL:

A major shift in preoperative radiotherapy was brought by Swedish rectal trial in the year 1997. This study had 1168 pts, randomisied to one of the arms , either single week of RT followed by surgery, or only surgery. On comparision of results , patients who received preoperative Radiotherapy had decreased local recurrence rate 11% vs 27%,[5] and improved overall survival 58% vs 48%. On long term follow up of 13 years, local recurrence and overall survival was 9% vs 26% , and 38% vs 30%[6].This study concluded that preoperative radiotherapy in a single week immediately followed by surgery for rectal cancer is found to be beneficial in terms of overall survival and cancer-specific survival and decrease in local recurrence rates[7] .

Next came the era of TME- Total Mesorectal Exicision, which is a sharp dissection along the planes of visceral and parietal endopelvic

fascia. It also involves removal of regional lymph nodes, while preserving the autonomic nerves. Multiple cohort and retrospective studies have shown that Total Mesorectal Exicixion is associated with lowered rates of pelvic recurrence compared to the less optimal blunt surgical dissection .

The **Dutch TME trial** ,in the year 2003 was the first trial to compare the results of surgey namely Total Mesorectal Exicision (TME) with and without short course radiation . This trial included 1861 pts, out of which 924 were randomized to receive either preoperative radiation followed by TME, 937 were randomised to TME alone. Analysis has shown that , local recurrence was significantly less in patients, who received preoperative RT plus TME compared with surgery alone (2.4% *vs* 8.2%, $P < 0.001$),[8] but there was not much difference in OS between the two groups. Sub group analysis also proved to be favourable to preoperative RT arm, showing decrease in local recurrence rates especially in patients with nodal positivity,[9] tumors located between 5-10 cm proximally from the anal verge, and patients with negative CRM-circumferential resection margins.

The **German CAO/ARO/AIO 94 trial** compared preoperative short course radiation and postoperative long-course chemo radiation . It

included T3 or T4 and/or node-positive tumors in locally advanced rectal cancers . Chemo radiotherapy consisted of continuous infusional fluorouracil (100mg/m2 per day for 5 days in the 1st and 5th week of radiation) of 50.4 Gy in 1.8 Gy/# in 28fractions.401 and 402 patients were randomisied to receive preoperative and postoperative chemo radiotherapy, respectively .Local recurrence in the preoperative group was 6% and 13% in postoperative group (P = 0.006).[10] Assessment of acute and long term toxicities have shown that Grade 3 or higher toxicity occurred substantially lesser in patients who received pre operative chemo radiation than post operative group. P value was (P = 0.001 and P = 0.01, respectively). (11)The main inference from the study has shown that the rates of sphincter preservation, Disease Free Survival and Overall Survival did not differ much between the two groups.

Another comparision between long and short course radiation regimen was done by **Polish randomized study,** which included patients with T3 and T4 rectal cancer. The results has shown promising rates of complete pathologic response in the group of patients receiving long- course chemo radiotherapy: 16% vs 1% of patients had complete pathologic response in the long-course and short-course arms respectively.[12] This study also showed that the sphincter preservation

rates were similar in both groups irrespective of the complete pathological states. Regarding the status of CRM- patients receiving long-course chemo radiotherapy had only 4% compared with 13% in the short-course group (P = 0.017)[13] Inspite of the higher positive CRM rates in short course arm, there was not much significant differences in rates of local recurrence, DFS or OS.

The **MRC CR07 and NCIC-CTG C016,** is a randomized trial in olving multiple centres. The population study comprised 1350 patients comparing the outcomes of preoperative short-course RT followed by surgery , and postoperative chemo radiation in selected patients with positivity of Cicumferrential Resection Margin. The outcome studied primarily was local recurrence. It demonstrated a substantial decrease in rates of local recurrence between patients receiving preoperative short-course regimen with hazard ratio 0.39($P < 0.0001$)[13]. And this was associated with a 6% absolute improvement in DFS at 3 years (P = 0.03)[14].These data again demonstrate the superiority of preoperative chemo radiotherapy.

In a review by Trans-Tasman Radiation Oncology Group Trial 01.04,randomized Trial of Short-Course regimen Versus conventional

Long-Course Chemo radiation comparing rates of local recurrence in Patients With T3 Rectal Cancer has shown that incidence of LR were 7.5%[15] for Short course RT and 4.4% for long course RT at the end of 3 years . But the p value was not significant. (16)

HYPOFRACTIONATED RADIATION:

The paucity of data regarding the optimal use of hypofractionated radiotherapy in rectal cancer for a population where 60% to 70% of cases usually present with locally and very advanced stages has been the idea behind the study protocol.

Hypofraction implies use of larger ose per fractionation with lesser number of fractions so as to deliver the equivalent biological effective dose (BED) in a shorter duration of time. The increase in dose per fraction (df) over the reference value of 2Gy , for an isoeffect , the total dose should be reduced. Due to low α/β ratio curves for late responding tissues, the curves are steeper than those of early reactions and for tumors, which have a high α/β ratio. Hence if df is increased to 5 Gy per

fraction and considering the α/β ratio for late reacting tissues to be 3Gy , then the total dose must be reduced from its reference value.

Hypofractionated schedules have the advantage of being more convenient for the patient , their care givers and also for the health care providers by sparing the essential resources.

POST NEOADJUVANT CHEMORADIATION LEVEL:

It has been shown by various studies that after neo adjuvant chemo radiation, CEA levels of <2.5 ng/mL and 5 ng/ mL[17] are associated with improvement in DFS and OS. But few other , studies has discerned this relation. Many studies focusing on correlation between predictive factors and long term outcomes do not rely on CEA levels. [18]So using this parameter to predict disease recurrence and survival still remains inconclusive.

RESPONSE ASSESSMENT AFTER NEOADJUVANT CHEMORADIATION:

The pathological response of tumor to neo adjuvant chemotherapy has shown to be the most important prognostic factor in terms of rectal

cancer recurrence.[19] Pathological Complete Respone is most strongly correlated with best outcomes .Many tumor regression grading systems are proposed and demonstrate a strong association between complete pathological response and their outcomes. Neo adjuvant chemo radiation reduces lymph node yield during surgery. The ratio of positive number of lymph nodes to total lymph nodes dissected is prognostic and presence of positive lymph node after neoadjuvant treatment is associated with poor prognosis[20].

The **MERCURY TRIAL** has studied the diagnosic importance of predicting the circumferential margin status by MRI. [21]The high resolution MRI accurately predicts the surgical margin status involvement by tumor. This study has shown the importance of identifying the patients with potentially affected margins and need for treating them with preoperative chemo radiation (22).

SURGERY:

The concept of total mesorectal excision in rectal cancer surgery has revolutionised the modern era of treatment . the practice of TME has reduced the rate of local recurrence and tumour associated mortality

and morbidity.The procedure involves the removal of the rectal tumour along with the entire mesorectum (radial margin). The mesorectum is the fatty tissue surrounding the rectum that contains the lymph nodes and main blood vessels that supply the rectum. Most of the local recurrence is likely to occur in the mesorectum, so removing the entire mesorectum,t reduces the chance of recurrence[23].

The healthy end of sigmoid colon is attached to the anal sphincter so normal bowel function can be resumed. Sometimes the anal sphincter cannot be saved and a permanent colostomy is needed. The location of the tumour, the size of the tumour and how far away the tumour is from the anal verge will determine whether the TME operation is done using either a low anterior resection or an abdominal perineal resection.

LOW ANTERIOR RESECTION (LAR):

A low anterior resection (LAR)is a procedure done to remove tumours in the upper two-thirds of the rectum. This procedure removes part of the descending colon, the sigmoid colon, all or part of the rectum and the mesorectum. A TME approach is used to remove the rectum and mesorectum.

ABDOMINAL PERINEAL RESECTION (APR):

An APR is a procedure done to remove low rectal tumours that invade the muscles around the anus. APR is also done when it is not possible to preserve the anal sphincter. This procedure removes part of the sigmoid colon, rectum, anus, mesorectum and anal muscles. The surgeon makes 2 incisions – one in the abdomen (using the TME approach) and one in the perineal region.

Two separate incisions are needed because of the 2 areas that are being removed. The rectal area is removed through the abdomen and the anal area is then completely removed and stitched up. Patients will then have a permanent colostomy. For this reason, APR is only done when there is no way to leave a margin of healthy tissue below the tumour margin[24].

LAPAROSCOPIC SURGERY FOR LOCALLY ADVANCED RECTAL CANCER:

Feasibility of laparoscopic surgery in the management rectal cancers has not been proven yet. But still, it has not become the standard

of care. The United Kingdom Medical Research Council Trial has compared conventional and laparoscopic assisted surgery in colorectal cancers. It has demonstrated equivalent results in terms of local control and survival benefit.[24] But the operating time is significantly longer and estimated blood loss is less in laparoscopic surgery as compared to open surgery. The positivity rates of circumferential resection margin was not significantly different between the studied groups[25]. The long-term outcomes of patients in this trial are awaited.

DISTAL RESECTION MARGIN (DRM):

The standard guideline recommendation for distal resected margin is 4- 5cm, measured from the distal edge of tumour. Many studies have shown that DRM <2 cm does not increase the recurrence rates or have a negative impact on the survival[26]. In situations of low rectal cancers located < 5 cm from the anal verge, 1 – 2 cm may be an acceptable margin.

Following treatment with neo adjuvant chemo radiation, the necessity of a margin for distal rectum of 2 to 3 cm is less significant than CRM.[27]

CICUMFERRENTIAL RESECTION MARGIN:

The standard cut- off point for the Circumferrential Resection Margin is still a matter of debate. Many studies has revealed <= 1mm margin as an acceptable cut off point[29 -31]. All have reported a significantly high rates of local recurrence and decreased survival in patients with inadequate CRM <= 1 mm.[32- 34]

TIMING OF SURGERY AFTER NEOADJUVANT TREATMENT:

After long course neo adjuvant chemo radiation , surgery is done usually after 6 weeks . This waiting period for 6 weeks is needed for adequate response to treatment to occur. But in case of short course radiation with high dose , surgery is usually done within 10 days of radiation. [35]Maximum within fourteen days radiation toxicity sets in. The irradiate bowel is removed during the surgery.

POST OPERATIVE CHEMOTHERAPY:

For locally advanced rectal cancers- stage II and III, the risk of local recurrence and metastasis remains high if only treated with surgery.

So to eradicate the micrometastasis, the role of adjuvant chemotherapy becomes crucial.

Most of the data on adjuvant chemotherapy regimens comes from extrapolating trials on colon cancer. The **MOSAIC TRIAL** was conducted on stage III colonic cancers .Chemotherapy regimen FOLFOX 4 as compared to 5FU+leucovorin has shown increase in DFS and OS.[36] In **X-ACT** study , the efficacy of capecitabine was compared with 5FU+ leucovorin , and it has shown equal efficacy in DFS and OS.[37]

EVALUATION OF MESORECTUM:

The completeness of TME should be evaluated by the pathologist. The sleeve of mesorectum to be examined completely for its quality of resection.It is mainly for distal 2/3 rd of rectal cancers.

TREATMENT DURATION TIME:

With long course of radiation , the time period required for neo adjuvant chemo radiation is 5.3 weeks. Patient has to wait for 6 weeks before

surgery. Then adjuvant chemotherapy is given after 3 to 4 weeks following surgery. So the total treatment time is around 40 weeks till completion of adjuvant 6 cycles chemotherapy.

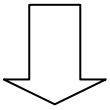
With short course radiation, the time required for radiation is one week. Surgery is done usually within 10 days of radiation. Adjuvant chemotherapy is given 3 -4 weeks following surgery. So the total treatment time is around 27 weeks. The significance of short course radiation is shorter duration of treatment and hence better patients compliance to treatment schedule.

Treatment breaks which occur during long course chemo radiation also has negative impact on local control of the disease and long term survival. Most of the patients default during the course of chemo radiation too, because of acute toxicities like cystitis and diarrhoea.

LONG COURSE CCRT REGIMEN:

Diagnosis , investigation evaluation of treatment plan

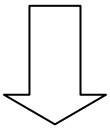
2 WEEKS



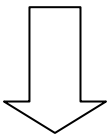
Concurrent chemo RT 50.4 Gy / 1.8 Gy/ # X 28 #

6WEEKS **+**

Chemotherapy= Capecitabine/Infustional 5FU/ Bolus 5 FU + Leucovorin



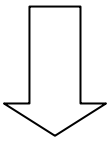
6WEEKS **Waiting period before surgery**



Total Mesorectal Excision

LAR/ APR

6WEEKS



Adjuvant chemo therapy 6 cycles

CAPEOX regimen

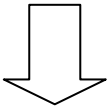
18 WEEKS **for 6 cycles of chemo therapy**

Totally : 36 to 40 weeks of treatment.

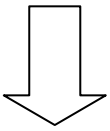
SHORT COURSE RADIATION REGIMEN:

Diagnosis , investigation evaluation of treatment plan

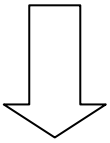
2 WEEKS



Short course radiation hypofraction 5Gy / # X 5 # = 25Gy



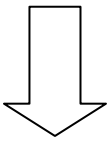
7 to 10 days **Waiting period before surgery**



Total Mesorectal Excision

LAR/ APR

4-5WEEKS



Adjuvant chemo therapy 6 cycles

CAPEOX regimen

18 WEEKS **for 6 cycles of chemo therapy**

Totally : 25 to 26 weeks of treatment

PREOPERATIVE VS POSTOPERATIVE RADIATION:

Main advantages of preoperative radiation , as compared to radiation given in the postoperative period are related to both response of tumor tissues and preservation of normal tissues. Although some trials have indicated that preoperative radiation or chemo RT is asscociated with increased sphincter preservation rates, but recent meta analysis of randomisied trials do not support it. (38)This may be due the surgeons perspective of removing the microscopic disease left behind after tumor downsizing. It also implies a good oncological practice **.**

CONCURRENT CHEMOTHERAPY WITH RADIATION:

Many randomized trials have studied the effectiveness of adding chemotherapy to radiation administrating either preoperatively or postoperatively. The benefits of adding chemotherapy either with pre or post operative radiation has increased the , local radiation sensitisation and systemic control of diseases (ie) the eradication of micro metastasis[39 – 41) .

A recent Cochrane review of six randomizied control studies showed that adding chemotherapy to preoperative radiation in resectable stage II/ III rectal cancers enhances the pathologic response rates and

improves the local control rates. But it did not have any effect on the overall survival, 30 day mortality , sphincter preservation rates and late toxicity(42-45).

KRAS MUTATION:

Approximately 40% of patients with colorectal cancers have mutations in the genes encoding KRAS. The presence of mutations in codons 12 and 13 in exon 2 o f KRAS gene predicts the nonresponsiveness to EGFR inhibition. Hence patients presenting with metastatic colorectal cancers, being considered for anti EGFR therapy should have their tumor tissue genotyped for presence of KRAS mutation before initiation of treatment. Several studies has shown that targeted agents produce negative impact on survival ,in patients with mutaed KRAS. So patients with KRAS mutation or NRAS mutation should not be treated with targeted either cetuximab or panitumumab.

Studies on colorectal cancer formation has shown that KRAS mutation occurs as an early event. Therefore a strong correlation exists between the mutation status , primary tumor and metastasis. It has been found that KIRSTEN RAS (KRAS) – mutation was associated with poor survival rates than patients with wild type KRAS . Presence of V600

BRAF mutation also signifies poor prognosis too. Data is insufficient to approve the use of anti EGFR therapy in the first line setting with systemic chemotherapy.

According to PRIME study , panitumumab was used along with FOLFOX regimen. It was used as a first line treatment in colorectal cancers. The results of this study showed that in patients with mutated KRAS , panitumumab had de trimental effects.

MICRO SATELLITE INSTABILITY:(MSI)

Testing for MSI should be considered for patients <= to 70 years of age with colorectal cancers.It should also be done on patients who are > 70 years of age , but meeting the Bethesda guidelines.

AIMS AND OBJECTIVES:

The aim of this study was to evaluate the efficacy of neo adjuvant short course Radiotherapy followed by surgery in locally advanced rectal cancers.

Primary Objectives :

To assess the immediate loco regional response rates of resectable stage II/III rectal cancers with neo adjuvant short course radiotherapy followed by surgery within 10 days.

Secondary objectives:

To assess acute toxicity to neo adjuvant short course radiation in locally advanced rectal cancer.

MATERIALS AND METHODS:

STUDY DESIGN:

This was a Single arm prospective study with a Phase III design.

STUDY DURATION:

OCTOBER, 2014 – August, 2015

STUDY CENTRE:

Department of Radiotherapy, Barnard Institute of Radiology & Oncology, Madras Medical college, Chennai.

SAMPLE SIZE:

30 consecutive patients with histopathologically proven adenocarcinoma of rectum who fulfilled the inclusion criteria were recruited in the study from the outpatient department.

The intent of treatment was to be radical, aiming for cure, considering their disease stage, co- morbidities and performance status.

ETHICAL COMMITTEE APPROVAL:

Approval from the institute ethical committee was obtained on 07.10.2014.

INFORMED PATIENT CONSENT:

All patients enrolled in the study were informed about the merits and demerits of participating in this study and signed an informed consent form in their regional language, which is Tamil.

METHODOLOGY:

Eligible patients will be treated with hypofractionation 5Gy per fraction for 5 days in one week, followed by surgery after 2 weeks. Postoperatively adjuvant chemotherapy is given for 6 cycles. The response to treatment and acute toxicity is to be assessed periodically.

Inclusion Criteria:

- Biopsy proven newly diagnosed adenocarcinoma of rectum.
- Age 18 - 65 years.
- T3 lesions less than or equal to 5 cm,N0 OR N+ disease.

- Performance status ECOG 0-2.
- Medically manageable co-morbidities.
- Signed informed consent prior to initiation of protocol.

Exclusion Criteria:

- Histopathology other than adenocarcinoma .
- Inadequate hepatic and renal functions, bone marrow reserve.
- Uncontrolled co-morbidities.
- Patient not consenting to radiotherapy/ surgery/chemotherapy at any point in the treatment.
- Previously received treatment for any other malignancy.

Sample Size: 30 patients

Investigation Details:

- . Detailed history elucidation.
- Complete physical examination by inspection, palpation.
- Biopsy from the primary tumour.

- Baseline-Complete blood count, liver function test, renal function test.
- X-ray chest PA view,
- ECG,
- Blood grouping &typing,
- Cardiac evaluation and fitness.
- Anaesthetic fitness for surgery,
- Colonoscopy,
- MRI- Pelvis-Plain &Contrast pretreatment.
- Tumor marker- CEA levels.
- Histopathology of surgical specimen.

Staging was done based on American Joint Committee staging manual 7th edition (for colorectal cancers).

PATHOLOGICAL STAGING OF THE SPECIMEN:

1. Gross description of the tumor and specimen.

2. Grade of the tumor.

3. Depth of penetration and extension to adjacent structures.

4. 5. Number of positive Lymph nodes.

6. Status of proximal ,distal and CRM.

7. Neoadjuvant treatment response.

8. LVI

9. Perineural invasion.

10. Number of tumor deposits.

CIRCUMFERRENTIAL RESECTION MARGIN:

It is defined as the closest radial margin , always measured in millimeters. It is between the deepest penetration of tumor tissue and resected edge of soft tissue around the rectum. Also from the edge of positive lymph nodes.CRM is identified by evaluating the outer surface of the resected specimen , which if often inked at. The examination of the specimen requires a bread loafing slicing technique.

TUMOR REGRESSION GRADING

Table 1

Description	Tumor regression grade
No viable cancer cells	0 (Complete response)
Single cells or small groups of cancer cells	1 (moderate response)
Residual cancer outgrown by fibrosis	2 (Minimal response)
Minimal or no tumor kill; extensive residual cancer	3 (Poor response)

.

TREATMENT PROTOCOL:

An informed consent was obtained from all patients. Before starting treatment, it was ensured that all patients had normal hematological/renal parameters and normal liver function tests. Adequate cardiopulmonary function that could tolerate radical surgery was also assessed before treatment. Comorbid conditions like diabetes and hypertension were evaluated thoroughly and treated with appropriate medications.

THERAPEUTIC PROTOCOL:

Short course radiation with hypofractionation 5 Gy / # X 5 # followed by TME within 10 days for T3 rectal cancers.

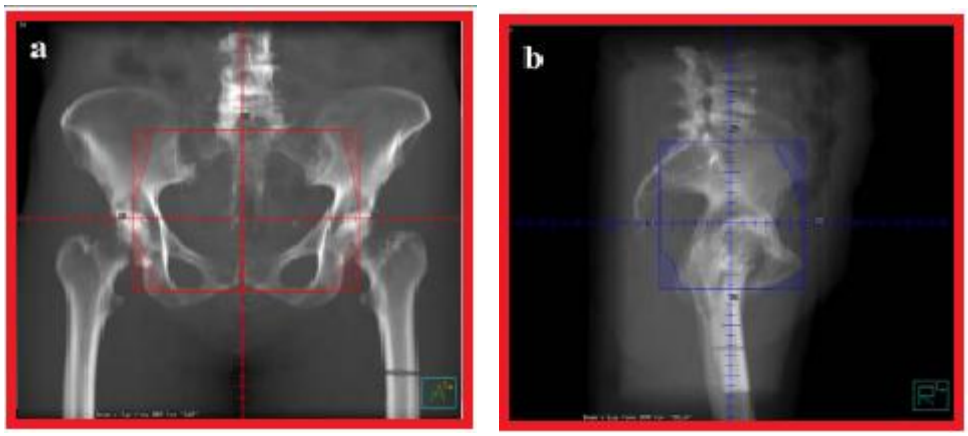
EBRT EQUIPMENT *Co – 60 Phoenix for Teletherapy*

SIMULATION AND TREATMENT DELIVERY

The treatment field was verified with PA simulator films in which the distal extension of the tumor was identified by placing a radio-opaque marker in the anal verge. The lateral portals were verified by lateral simulator films.The treatment plan was evaluated with and without wedges in TPS planning system and optimal treatment plan was selected from isodose pattern All patients were positioned in the prone position only with full bladder during external RT to exclude a greater extent of the small bowel from the treatment field.

SIMULATION FILM USED:

Figure 16: Simulation Film



RT SCHEDULE

All patients were treated with hypofractionated dose 500cgy/ # by three field 1 PA portal(168 cgy) / 2 lateral portals (166 cgy each) to a total dose of 500cgy delivered from Monday, Wednesday to Friday in a week .

RADIOTHERAPY TECHNIQUE:

Radiotherapy was delivered by three field technique to the pelvis with a telecobalt machine. 5 # was delivered in 5days in one week. The clinical target volume including the tumor, internal iliac nodes, obturator nodes , and the anal canal for adequate clearance received the calculated dose of 25 Gy. Organ at risk was given due consideration in treatment planning process. All three fields were treated on all 5 days of planned radiation with equal dose distribution.

RADIATION MARGINS:

POSTERO-ANTERIOR FIELD:

Table 2

RT PORTAL MARGINS FOR EBRT PA PORTAL	
SUPERIOR	**L5 S1 INTERFACE**
INFERIOR	**2 CM BELOW DISTAL MARGIN OF TUMOR**
LATERAL	**2CM LATERAL TO BONY PELVIS**

LATERAL FIELD:

Table 3

RT PORTAL MARGINS FOR EBRT LATERAL PORTAL	
SUPERIOR	**L5 S1 INTERFACE**
INFERIOR	**2 CM BELOW DISTAL MARGIN OF TUMOR**
ANTERIOR	**POSTERIOR BORDER OF PUBIC SYMPHYSIS**
POSTERIOR	**PRESACRAL BAY – S2**

BED VALUE CALCULATIONS FOR EBRT :

According to the linear –Quadratic model the formula for calculating the biologically effective dose is

$$BED = Nxd\,[1+d/(\alpha/\beta)] - K[T-T_0]$$

Where N - no of fractions

d - dose per fraction

α/β -dose at which the linear and quadratic cell kills are equal

k -constant (Dose required /day to counter act proliferation)

T - Over all treatment time

T_0 – Onset time for proliferation

Calculation of biologically equivalent doses to 2 Gy /# for the three most commonly used fractions.

Table 4

Biologically equivalent doses to 2 Gy / #			
	25 Gy in 5Gy/#	45 Gy in 25 #	50.4 Gy in 28 #
Tumor control with Time correction	35.7	28.1	30.4
Late issue toxicity	40.0	43.2	48.4

Biologically equivalent doses (2 Gy per fraction) along with a factor for time correction = biologically equivalent doses (2 Gy per fraction) – 0.6 Gy (T-7),

Where T = overall treatment time in days.

In this equation ,it is assumed that 0.6 Gy is lost per day due to tumor repopulation starting after 7 days from the beginning of radiation.

RESPONSE EVALUATION AND SURGERY

Within 10 days of last fraction of radiation, patients are taken up for surgery- TME either low anterior resection or abdomino perineal resection. Histologic analysis of surgical specimens was done to assess the extent of CRM-circumferrential resection margin status ,lymph node status and the involvement of proximal and distal rectal margins.

Operative complications included bladder, small bowel, ureteral or vascular injuries. Any surgery related adverse event occurring within 30days from the intervention was recorded as postoperative complication.

TOXICITY ASSESSMENT:

Patients were reviewed every day before radiation for any acute toxic reactions. Reactions like skin desquamation, cystitis, and proctitis etc. were recorded and graded based on RTOG acute radiation morbidity criteria. Careful attention was given for maintenance of hydration, adequate dietary intake and good personal hygiene.

Hematological and renal parameters were assessed before and after radiation. And before surgery. Anaesthetist opinion was obtained.

SIDE EFFECT MANAGEMENT:

- In female patients , symptoms of vaginal stenosis can occur. So they should be instructed to use vaginal dilators .
- In case of young males and females, counselimg should be done regarding infertility risks. They should be given information regarding sperm and oocyte banking.

STATISTICAL ANALYSIS:

The patient factors, tumor factors, response to treatment, and toxicities were thoroughly analyzed. The results are expressed in percentage. Since this study is single armed one and also the sample size was only 30, the levels of significance cannot be commented on.

FOLLOW UP:

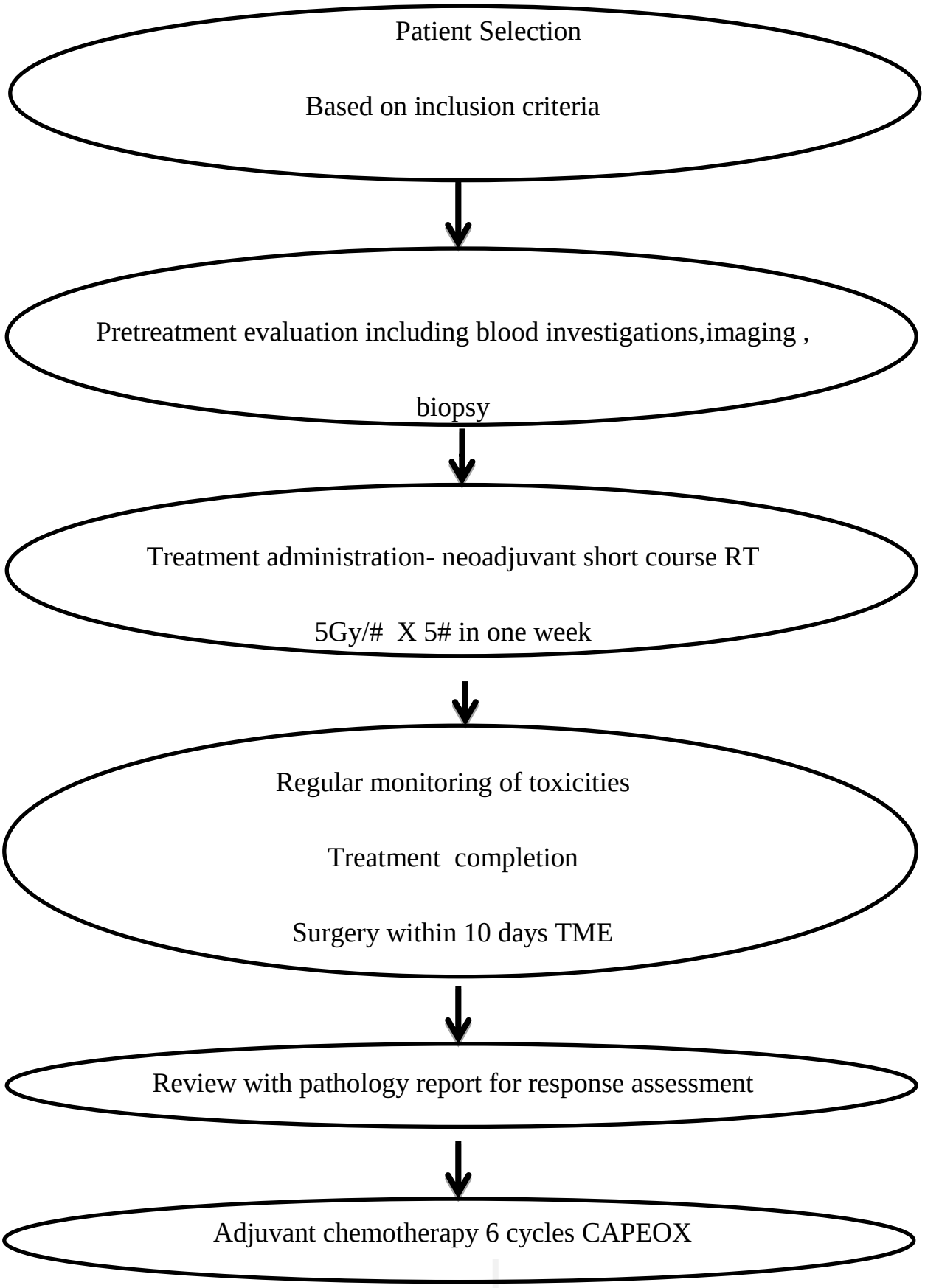
- Patients after completion of surgery was discharged from the hospital and was to review after 4 weeks for adjuvant chemotheraphy.
- CEA levels were done after surgery and there after three monthly.
- Imaging was done when indicated clinically

- Counselling to the patient and attender, rehabilitation, usage of colostomy bags and cleaning of the same was given.

MANAGEMENT OF LATE SEQUELE OF TREATMENT:

Patients treated with pelvic surgery and radiation can have symptoms of chrnic diarrhea or incontinence. They should be managed symptomatically with anti- diarrhea drugs, stool bulk forming agents, diet manipulation and protective undergarments. Radiation cystitis , increased frequency and urgency of micturation are managed symptomatically with bladder irrigation techniques.

TREATMENT PROTOCOL



RESULTS AND ANALYSIS

Out of 30 patients recruited for the study, 29 pts completed their entire treatment protocol and were available for analysis of results. One patient underwent diversion colostomy only, followed by palliative chemotherapy.

PATIENT CHARACTERISTICS:

AGE DISTRIBUTION:

43% of the patients belonged to the age group 51- 60yrs, followed by 41 -50yrs. The mean age of presentation was 55.5yrs. The youngest patient age was 35yr and the oldest was 67 yrs.

AGE DISTRIBUTION OF THE STUDY POPULATION

Table 5

AGE GROUP	NUMBER	PERCENTAGE
31- 40yrs	6	20%

41 -50yrs	9	30%
51-60yrs	13	43%
61-70yrs	2	7%

GENDER:

The gender distribution in the study population is dominated male population. This study has 16 male patients followed by 14 female patients.

GENDER DISTRIBUTION OF THE STUDY POPULATION

Table 6

SEX	NO. OF PATIENTS	PERCENTAGE
MALE	16	53.33%
FEMALE	14	46.67%

PERFORMANCE STATUS:

All patients in this study had a general performance status of ECOG (Eastern Cooperative Oncology Group) grade 0 or 1.

ECOG PERFORMANCE STATUS

Table 7

ECOG	NO.OF PATIENTS	PERCENTAGE
ECOG 0	18	60%
ECOG 1	12	40%

SYMPTOMS AND SIGNS:

Among the study patients the most common presenting symptom was bleeding per rectum followed by difficulty in defecation.(figure no:6

SYMPTOMS/SIGNS

Table 8

PRESENTING SYMPTOMS/SIGNS	NUMBER	PERCENTAGE
PAIN DURING DEFECATION	12	40%
BLEEDING PER RECTUM	16	53%
DIFFICULTY IN DEFECATION	18	60%
LOWER ABDOMINAL PAIN	12	40%
INCREASED FREQUENCY OF STOOLS	7	23%
LOSS OF WEIGHT	4	13%

HISTOLOGICAL DIFFERENTIATION:

Most of the patients in the study belonged to moderately differentiated histology followed by well differentiated on

HISTOLOGICAL DIFFERENTIATION

Table 9

HISTOLOGICAL DIFFERENTIATION	NUMBER OF PATIENTS	PERCENTAGE
WELL DIFFERENTIATION	9	30%
MODERATELY DIFFERENTIATED	16	53.33%
POORLY DIFFERENTIATED	5	16.67%

SIZE OF THE TUMOR:

The estimation of tumor size was by clinical and radiological examination. Imaging modality used was MRI .

SIZE OF TUMOR

Table 10

SIZE OF THE TUMOR	NO. OF PATIENTS
2-4cm	15 (50%)
4– 5 cm	15 (50%)

.

As per the inclusion criteria, only patients having size of the tumor mass less than 5 cms were included. 50 % of them had tumor size between 2- 4 cms and 50 % of them between 4 – 5 cms**.**

HISTOLOGIC GRADE:

Most common histological grade was grade II , followed by grade I tumors.

HISTOLOGICAL GRADE

Table 11

GRADE	NO. OF PATIENTS
GR I	11(36.67%)
GR II	12 (40%)
GR III	7 (23.33%)

TYPE OF SURGERY:

Out of 30 patients , 29 underwent curative resection. One patient had only diversion colostomy due to adherence to adjacent structures.40 % of patients underwent Low anterior resection.56% of patients had Abdomino perineal resection. Selection of patients for either of the

procedures was based on distance of the tumor from anal verge and also the oncological principle of achieving adequate distal margin status and

TYPE OF SURGERY

Table 12

TYPE OF SURGERY	NUMBER	PERCENTAGE
Low anterior resection	12	40%
Abdominoperineal resection	17	56.67%
Hartmans procedure	1	3.33%

STATUS OF CIRCUMFERENTIAL RESECTION MARGIN:

All patients had adequate circumferential resection margin status. None of them had positivity of CRM less than one centimeter.

CIRCUMFERRENTIAL MARGIN STATUS

Table 13

CIRCUMFERRENTIAL RESECTION MARGIN	NO.OF PATIENTS	PERCENTAGE
< =1 CM	NONE	O%
>1 CM	29	96.67%

PATHOLOGICAL T STAGE: y p (T) stage

For patients who had minimal involvement of perirectal tissues, after neoadjuvant radiation they were downstaged to T2 lesion from T3 lesion.

Y P(T) STAGE

Table 14

TUMOR STAGE	NO.OF PATIENTS	PERCENTAGE
T2	9	30%
T3	20	66.67%

DISTANCE OF LOWER BORDER OF TUMOR FROM ANAL VERGE:

Most of the tumors were 3 to 6 cms from the anal verge, around 46.67 percent. 26.67 5 of the patients had tumors in the upper part of the rectum , with distal margins more than 6 cms from the analverge.

DISTANCE FROM ANAL VERGE

Table 15

DISTANCE FROM ANALVERGE	NUMBER OF PATIENTS	PERCENTAGE
0 – 3 cms	8	26.67%
3 – 6 cms	14	46.67%
> 6 cms	8	26.67%

NO OF RETRIEVED MESORECTAL LYMPHNODES:

Yield of lymph nodes in the mesorectum after neoadjuvant treatment is usually less compared to afferent surgery. Median number of lymph nodes resected was 7 LNs.

NUMBER OF LYMPH NODES DISSECTED

Table 16

NO OF NODES DISSECTED	NUMBER OF PATIENTS	PERCENTAGE
0 – 5	11	36.67%
5 – 10	13	43.33%
> 10	5	16.67%

NODAL STATUS:

Nodal staging after neoadjuvant radiation is usually difficult. 60% of the patients had N0 disease.

NODAL STAGING.

Table 17

NODAL STATUS	NO.OF PATIENTS	PERCENTAGE
N0	18	60%
N_+	12	40%

INTERVAL BETWEEN RADIATION AND SURGERY:

Most of the patients were taken up for surgery within 10 days. Median number of days between last day of radiation and surgery **is 8 days**

TUMOR SIZE Vs RESPONSE

Table 18

Tumor size	Response		
	CRM 1-1.5 CM	CRM >1.5 CM	T2 DISEASE
2-4 CM	2	4	9
4- 5 CM	10	4	-

RESPONSE VS ISTANCE FROM ANAL VERGE

Table 19

DISTANCE FROM ANAL VERGE	Response		
	CRM 1-1.5 CM	CRM >1.5 CM	T2 DISEASE
0 – 3 CM	5	2	0
3 – 6 CM	4	3	7
> 6 CM	3	3	2

HISTOLOGICAL DIFFERENTIATION Vs RESPONSE

Table 20

HISTOLOGIC DIFFERENTIATION	Response		
	CRM 1-1.5 CM	**CRM >1.5 CM**	**T2 DISEASE**
WELL DIFFERENTIATED	3	3	3
MODERATELY DIFFERENTIATED	5	5	6
POORLY DIFFERENTIATED	4	-	-

PERFORMANCE STATUS Vs RESPONSE:

The ECOG performance status among the study patients did not show much difference in the response rates, as the study patients are in the ECOG 0 OR ECOG 1.

GENDER Vs RESPONSE:

As the male population dominated the study 75% of the males had complete response in contrast to 66% of the females. As the male and female ratio was not equivalent it cannot be considered as significant.

TREATMENT RELATED ACUTE TOXICITIES:

As expected with pelvic radiation , toxicity to bladder , small bowel and pelvic bone marrow was not seen in this study. Mainly these type of complications occur during long course radiation.

SYSTEMIC TOXICITY:

The treatment related systemic toxicity was assessed with CTCAE V 4.03 and treated accordingly. Most of the patients experienced nausea and diarrhea.

NAUSEA:

80% of the study population developed loss of appetite grade 1 nausea during their treatment course.20% of them developed grade 2 nausea.

VOMITING:

23% of the patients had grade 1(1 or 2 episode) of vomiting during radiation. Only 6% of the patients had grade 2(3 or 4 episodes) of vomiting managed by Oral Rehydration Salt and Inj.Ondansetron iv bid for 3 -5 days. Intravenous fluids were given whenever necessary.

DIARRHOEA:

Only 30% of the patients had grade 1 diarrhoea *(many of them had preexisting diarrhea). Mostly the diarrhea was managed conservatively.

SYSTEMIC TOXICITY

Table 21

TOXICITY	GRADE I	GRADE II
NAUSEA	24	6
VOMITING	7	2
DIARRHOEA	9	4

NAUSEA:

Since the radiation included only the pelvic cavity , and not much of small bowels into the field , few patients had nausea and vomiting. it was managed conservatively with

1.IV fluids to correct dehydration, if any.

2.Metoclopramide 40 mg PO every 4–6 hours for 4 days.

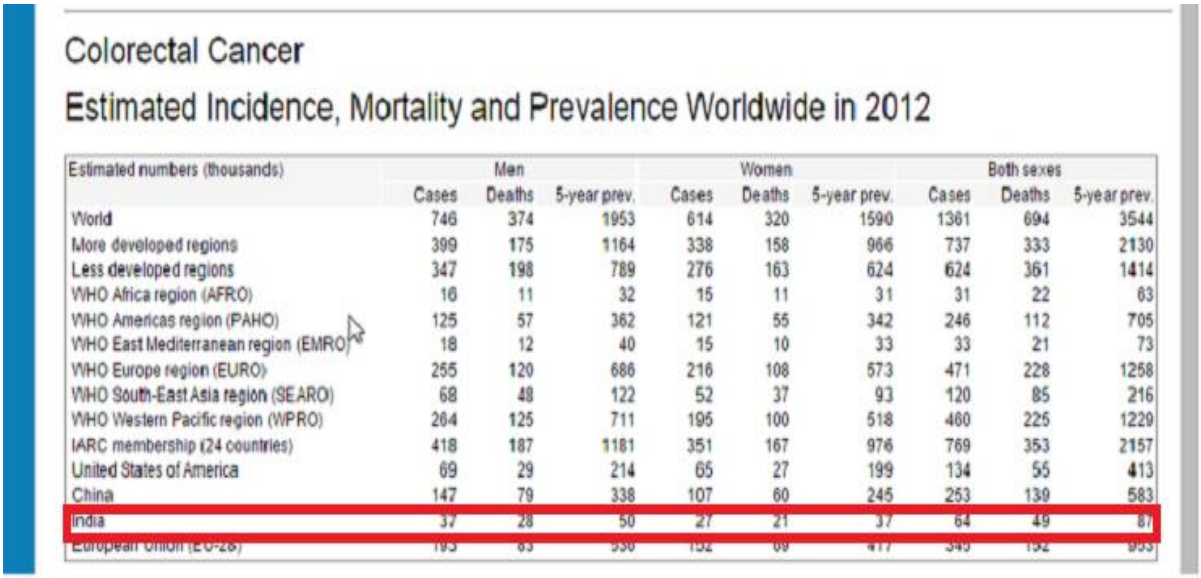
3.Ondansetron 4-8 mg IV BD for 4 days.

DIARRHOEA:

Diarrhea is a common complication in any pelvic radiation regimen. The grade 1 and grade 2 reactions were managed by plenty of fluid intake, and IV fluids in case of dehydration not corrected by oral rehydration alone. Antispasmodics and anti-motility agents were used to reduce the frequency of stools and to manage the abdominal cramps and pain. Regular monitoring of the biochemical parameters was done.

GLOBOCON 2012

Figure :1- estimated incidence, mortality and prevalence.



Colorectal Cancer

Estimated Incidence, Mortality and Prevalence Worldwide in 2012

Estimated numbers (thousands)	Men			Women			Both sexes		
	Cases	Deaths	5-year prev.	Cases	Deaths	5-year prev.	Cases	Deaths	5-year prev.
World	746	374	1953	614	320	1590	1361	694	3544
More developed regions	399	175	1164	338	158	966	737	333	2130
Less developed regions	347	198	789	276	163	624	624	361	1414
WHO Africa region (AFRO)	16	11	32	15	11	31	31	22	63
WHO Americas region (PAHO)	125	57	362	121	55	342	246	112	705
WHO East Mediterranean region (EMRO)	18	12	40	15	10	33	33	21	73
WHO Europe region (EURO)	255	120	686	216	108	573	471	228	1258
WHO South-East Asia region (SEARO)	68	48	122	52	37	93	120	85	216
WHO Western Pacific region (WPRO)	264	125	711	195	100	518	460	225	1229
IARC membership (24 countries)	418	187	1181	351	167	976	769	353	2157
United States of America	69	29	214	65	27	199	134	55	413
China	147	79	338	107	60	245	253	139	583
India	37	28	50	27	21	37	64	49	87
European Union (EU-28)	193	83	530	152	69	417	345	152	953

Figure: 2 Male and female distribution in various regions.

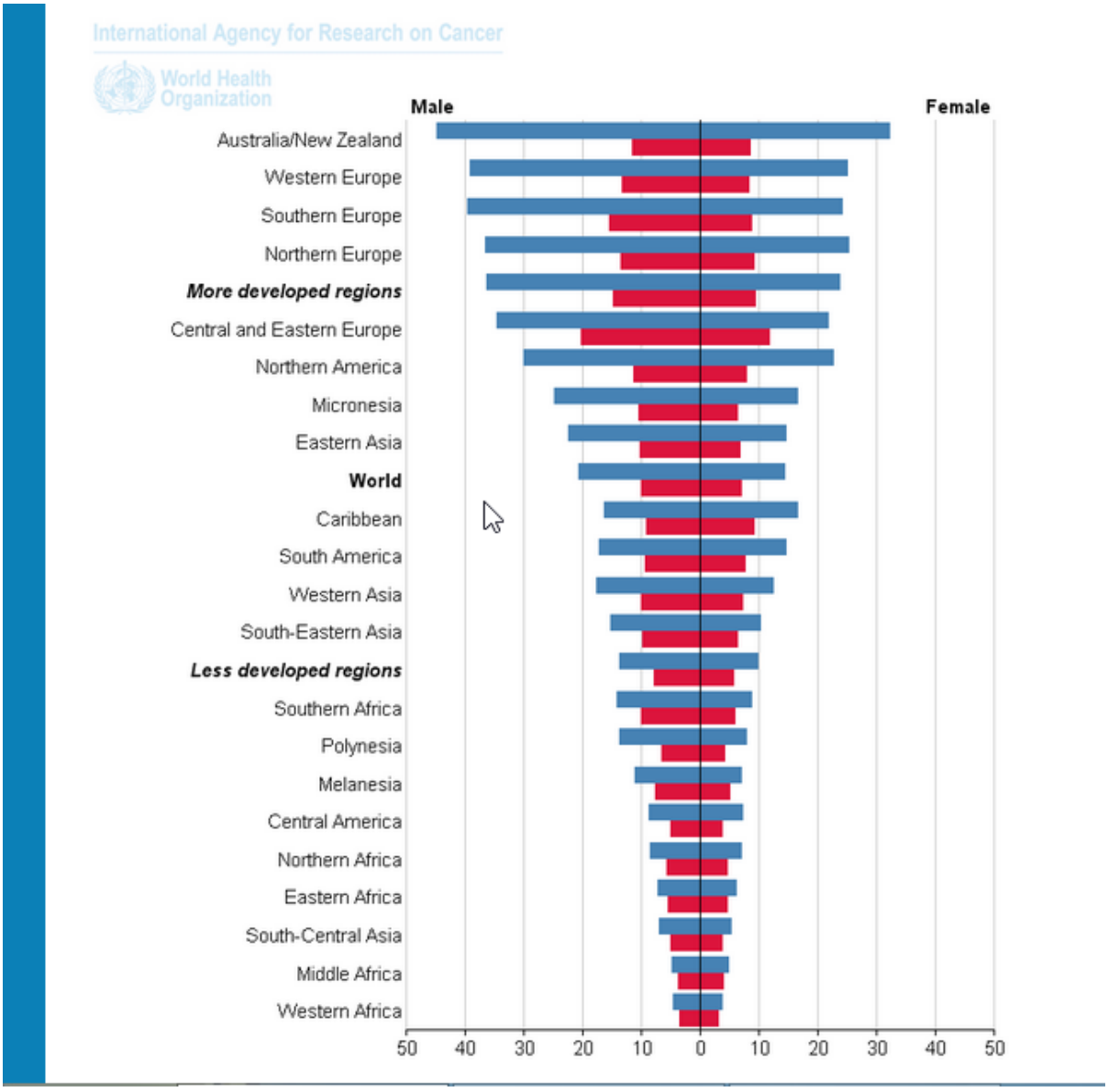


Figure :3 colorectal cancer incidence in men.

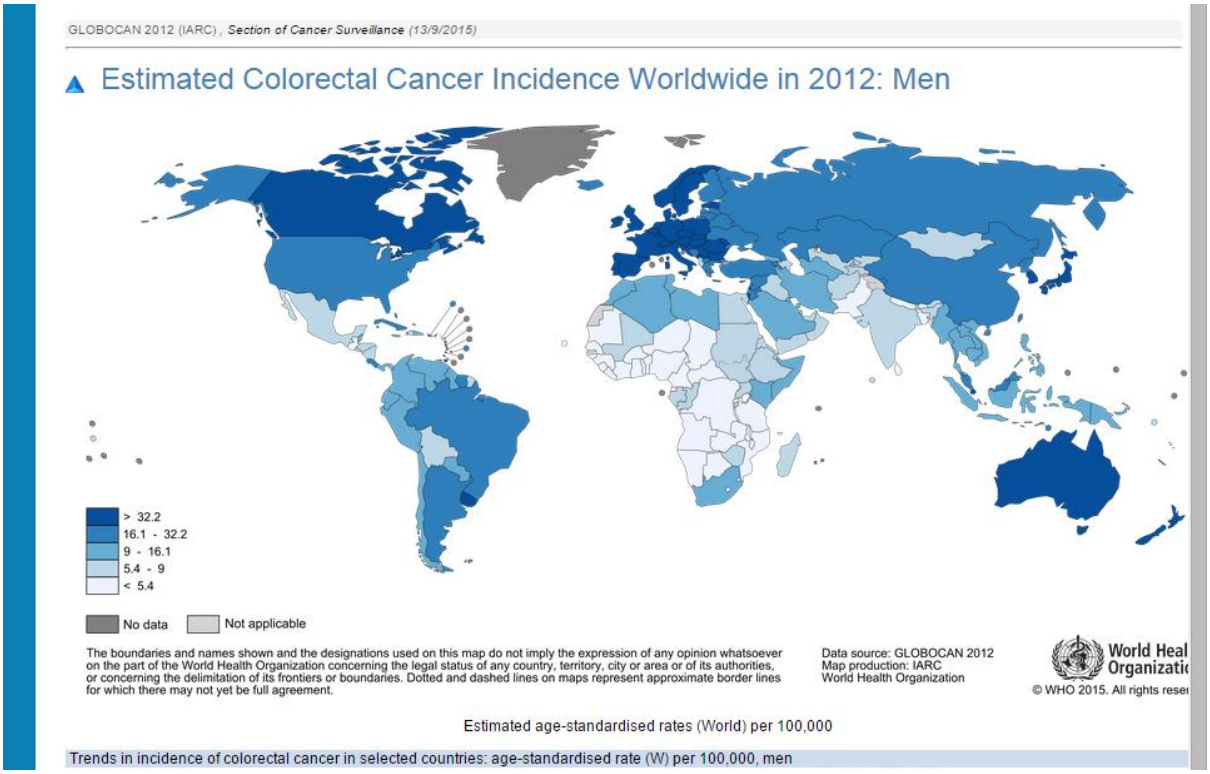


Figure : 4 colorectal cancer incidence in female.

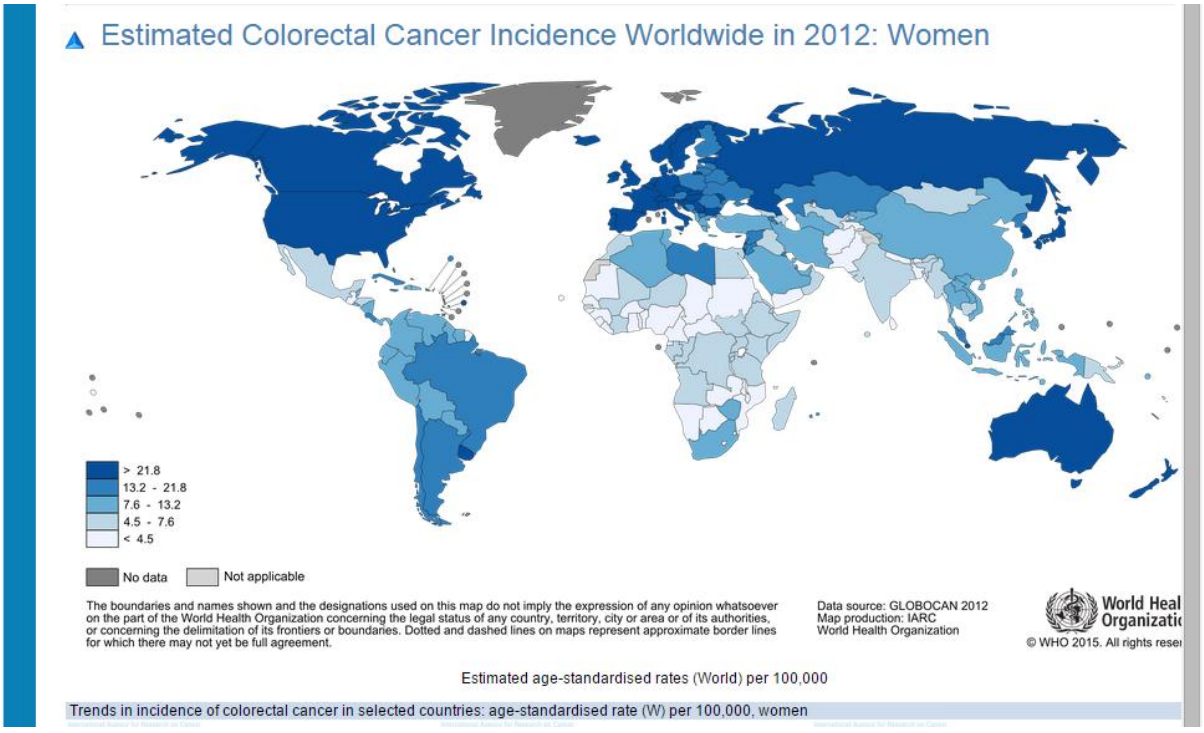


Figure: 6 LINEAR QUADRATIC MODEL

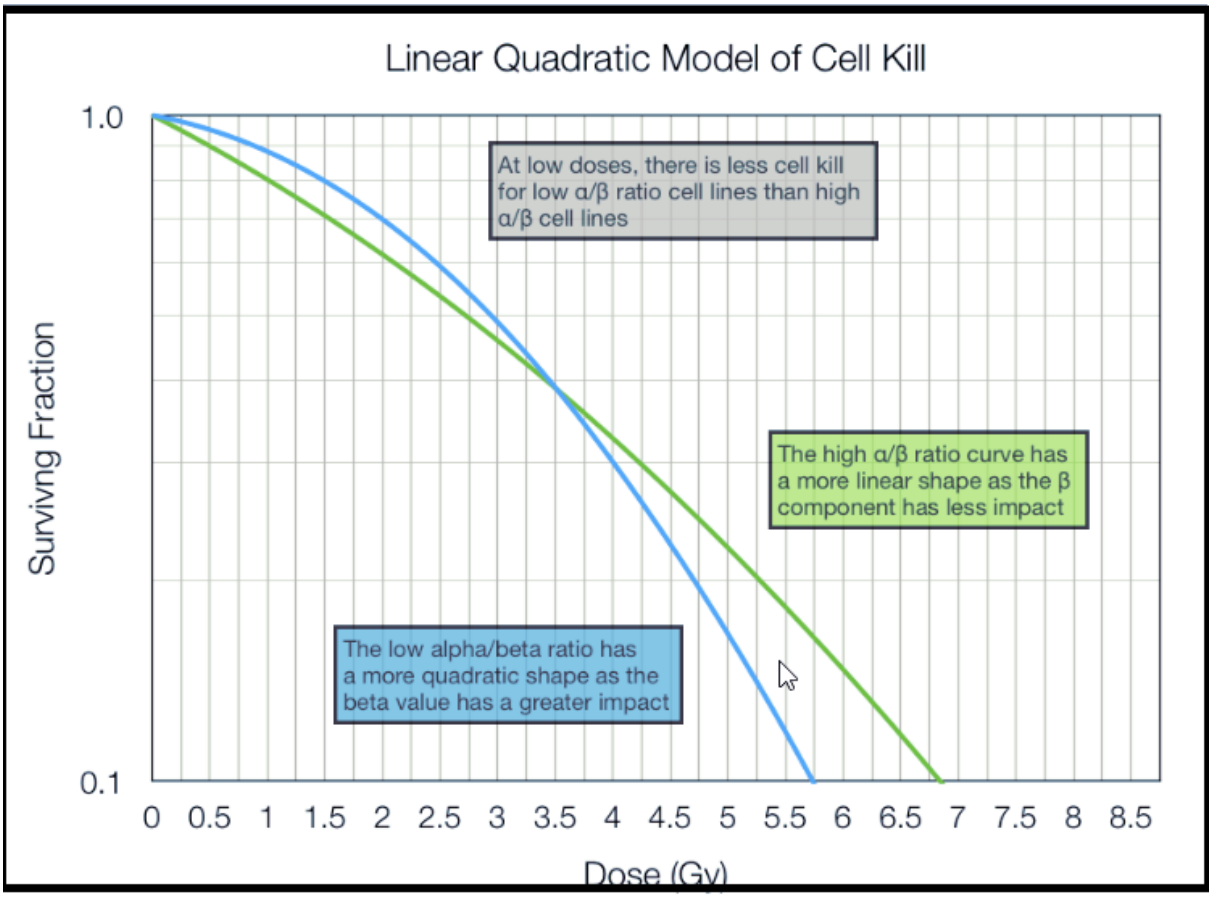


Figure : 7 PLANE OF TOTAL MESORECTAL EXCISION

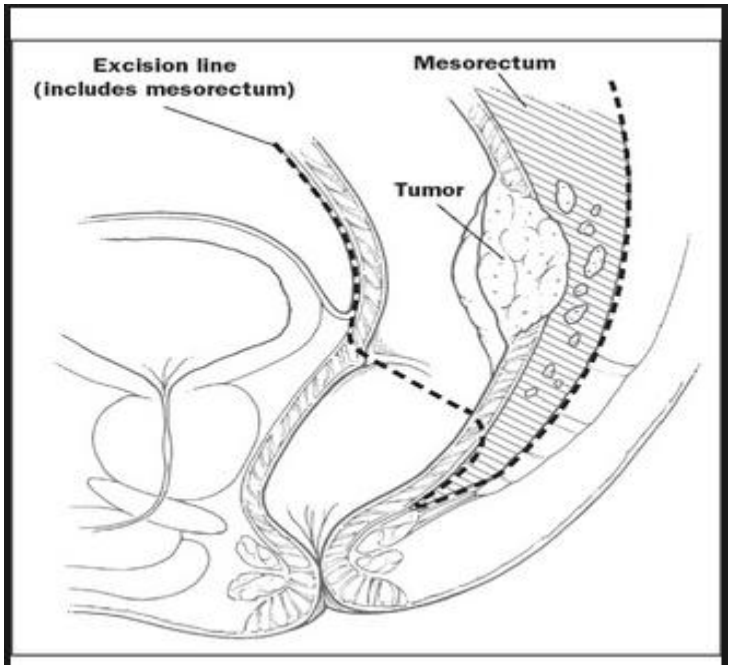


Figure : 8 CIRCUMFERRENTIAL RESECTION MARGIN

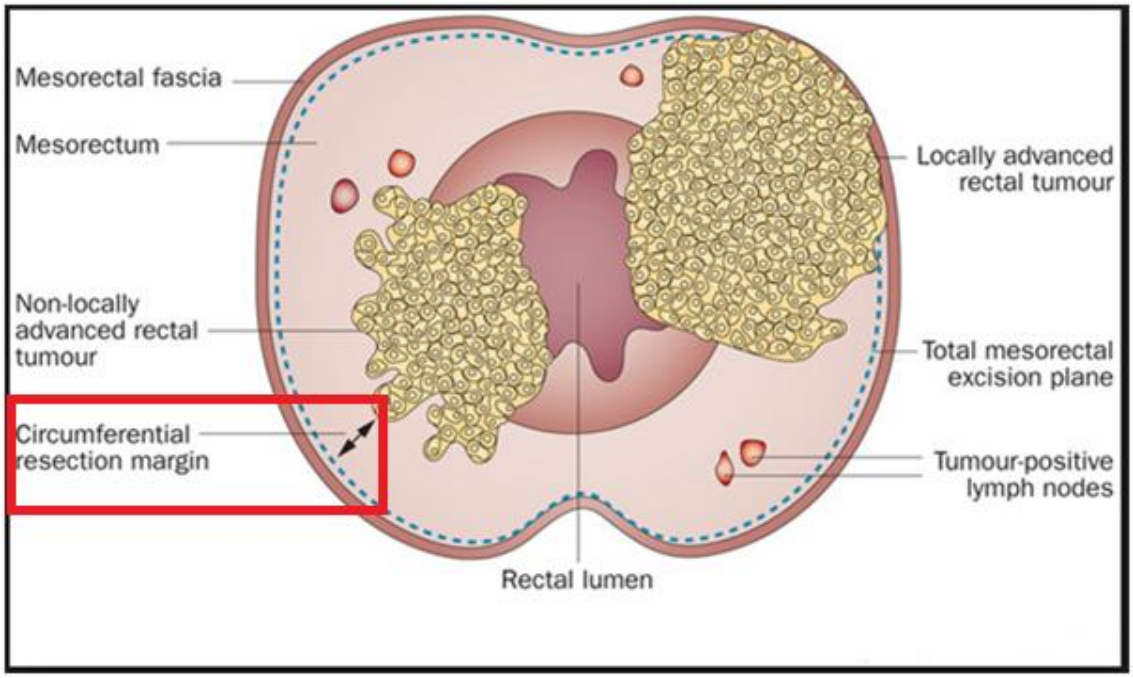


Figure : 9 MRI PICTURE SHOWING INVOLVEMENT OF CRM

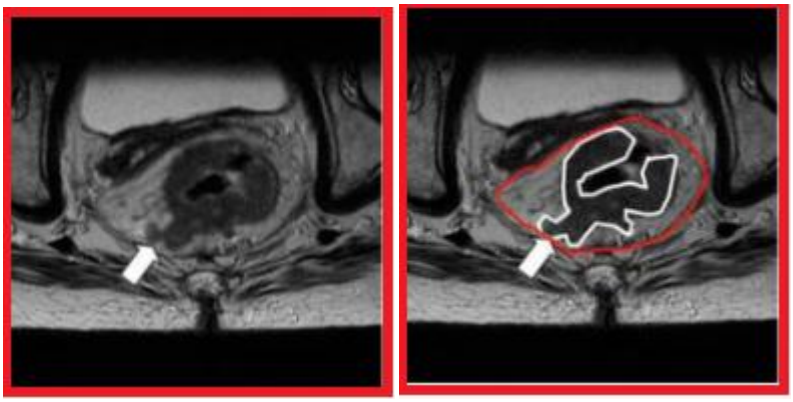


Figure : 10 KRAS MUTATION

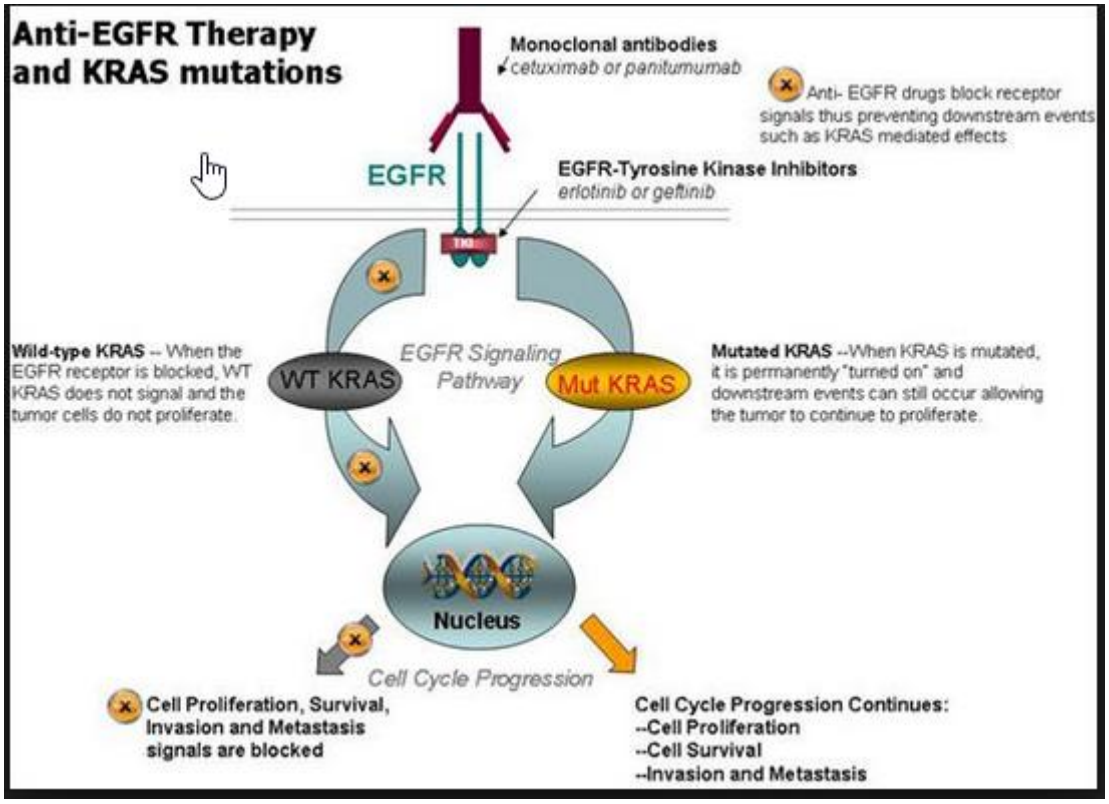


Figure : 11 MOLECULAR PROFILING

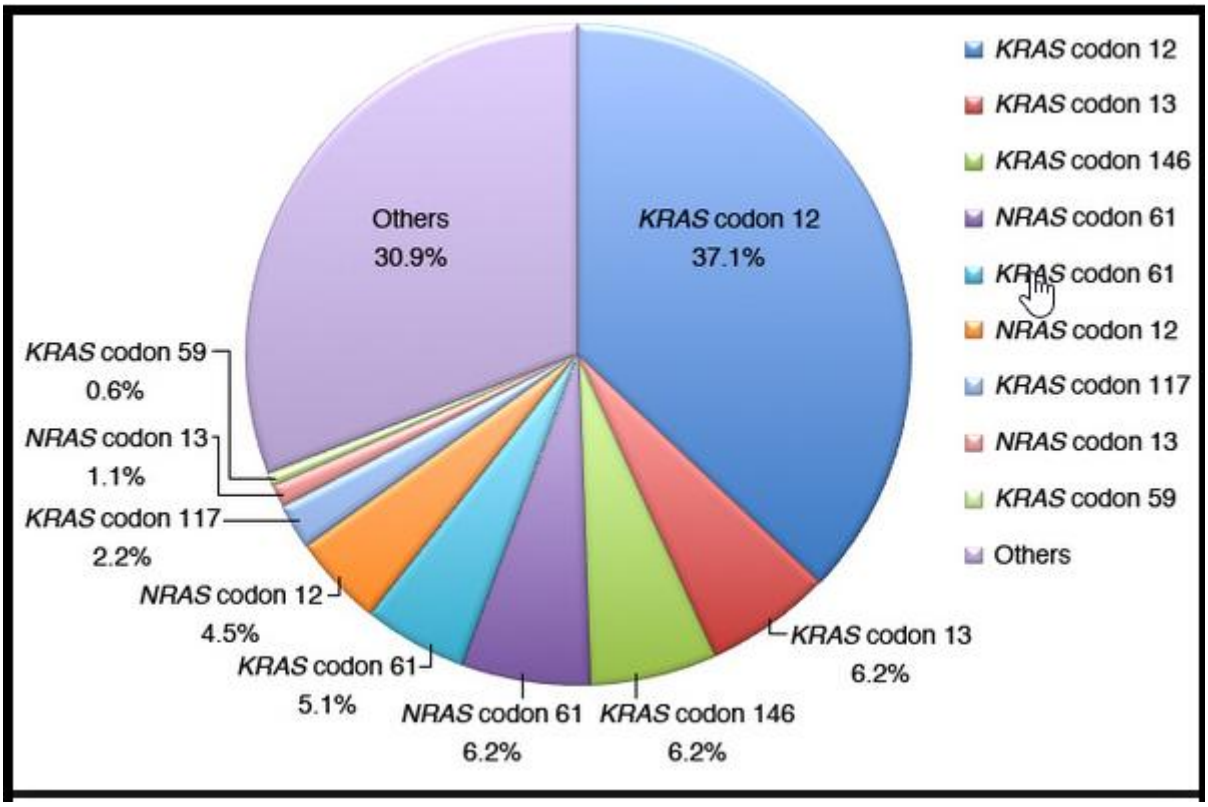


Figure : 12 COLOSCOPY SHOWING MASS LESION

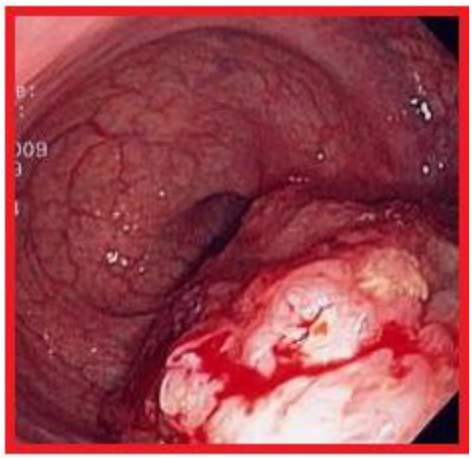


Figure : 13 RESECTED SPECIMEN

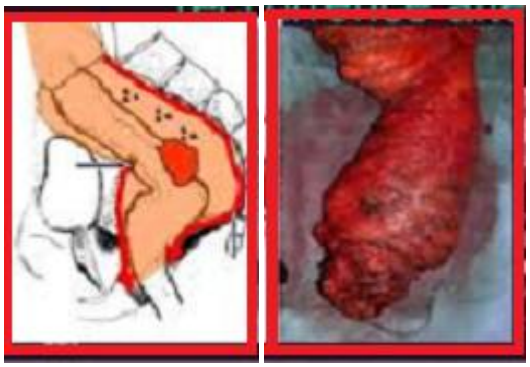
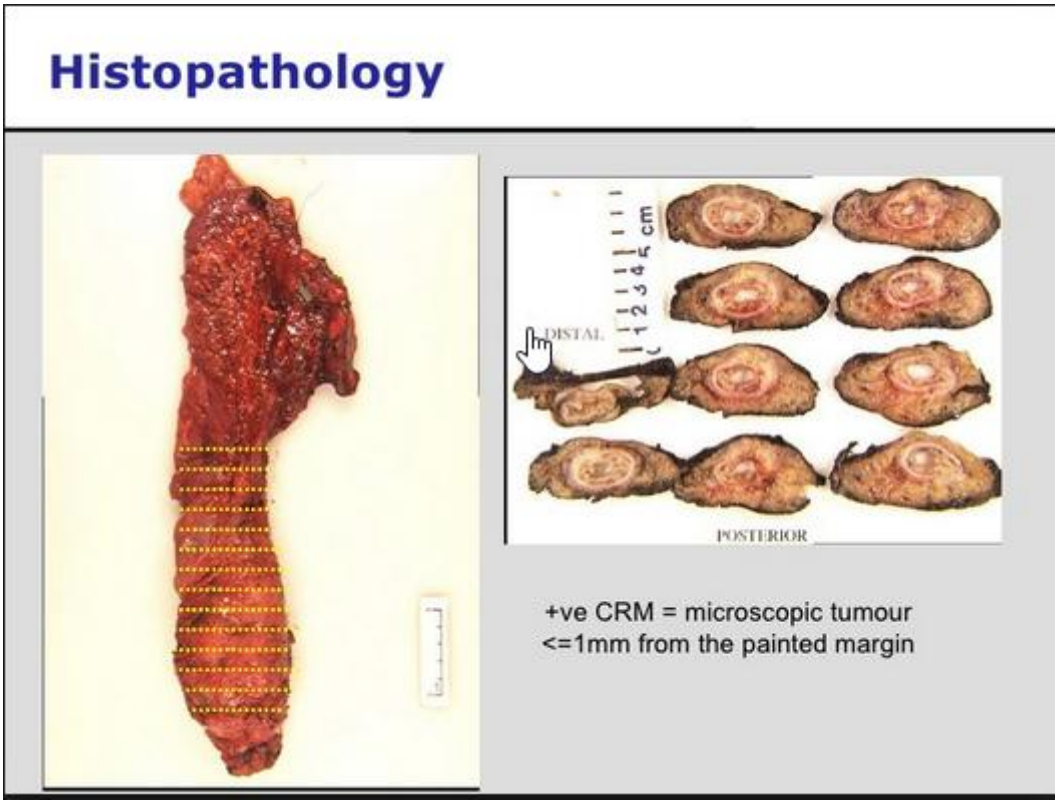


Figure : 14 INKING OF THE SPECIMEN FOR CRM

Figure : 15 BREAD LOAFING SLICING TECHNIQUE



OPERATIVE PICTURES

Figure : 20 SHARP DISSECTION ALONGMESORECTUM

Figure : 21 IDENTIFYING THE PROXIMAL MARGIN

Figure : 22 RESECTED SPECIMEN

Figure : 23 ORIENTING THE SPECIMEN

EVALUTION OF SPECIMEN FOR CRM

Figure : 24

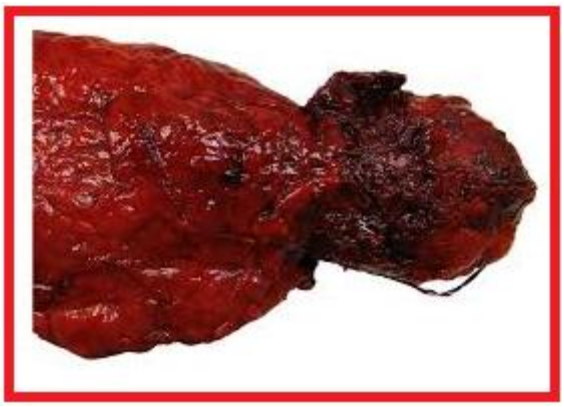
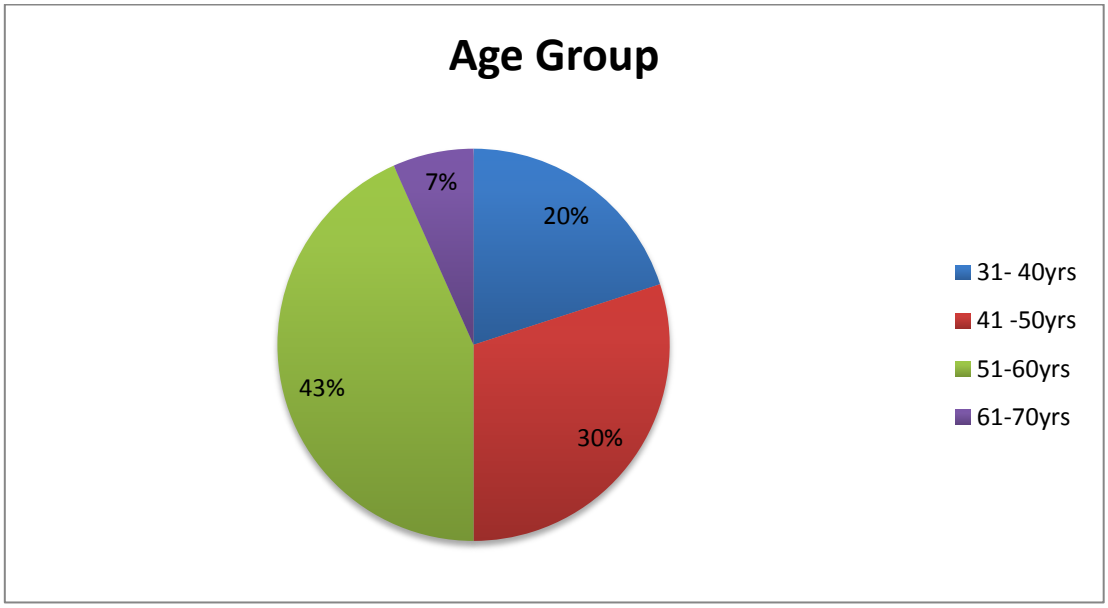


Figure : 25

Figure: 26



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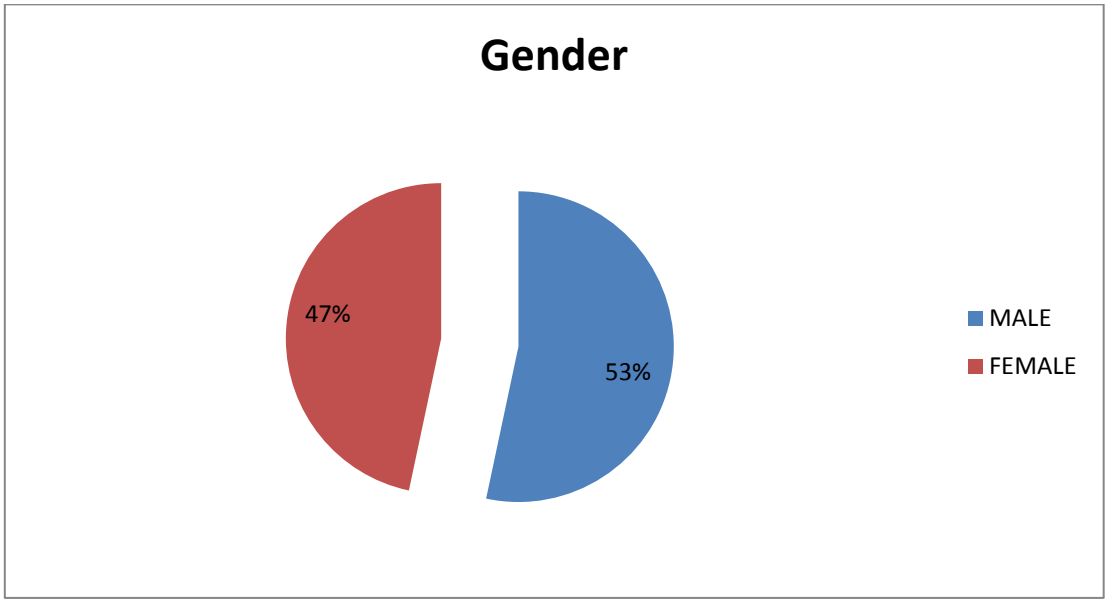

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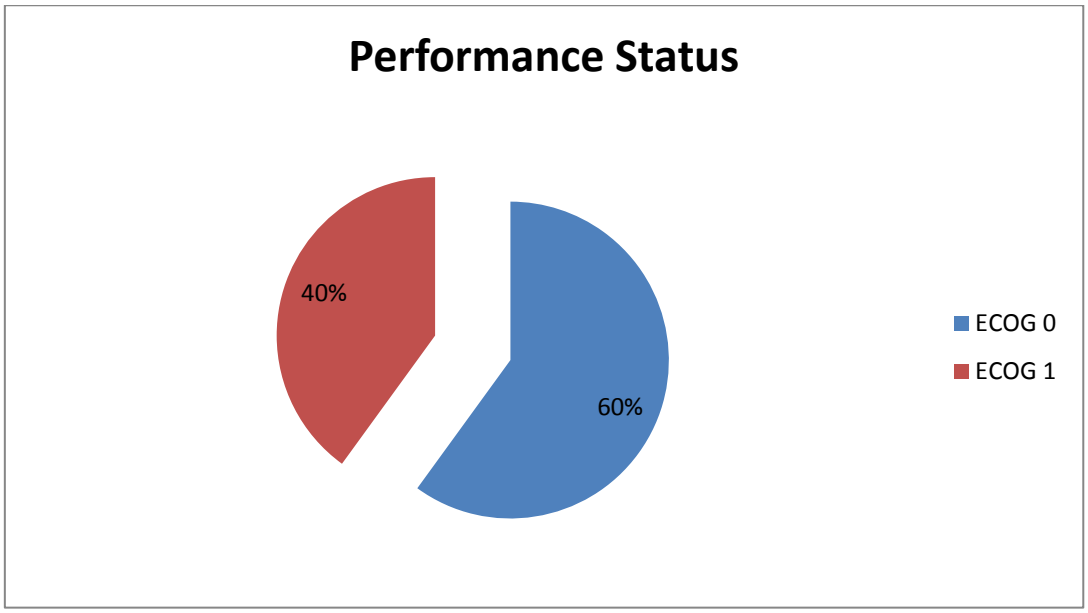


Figure: 29

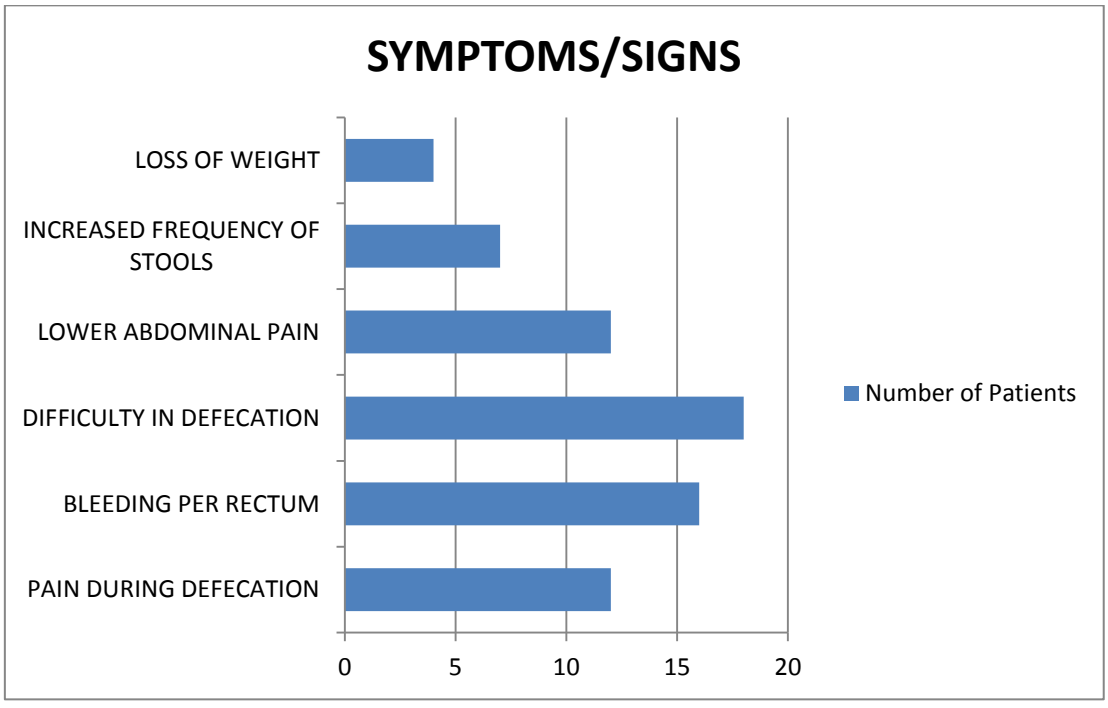


Figure: 30

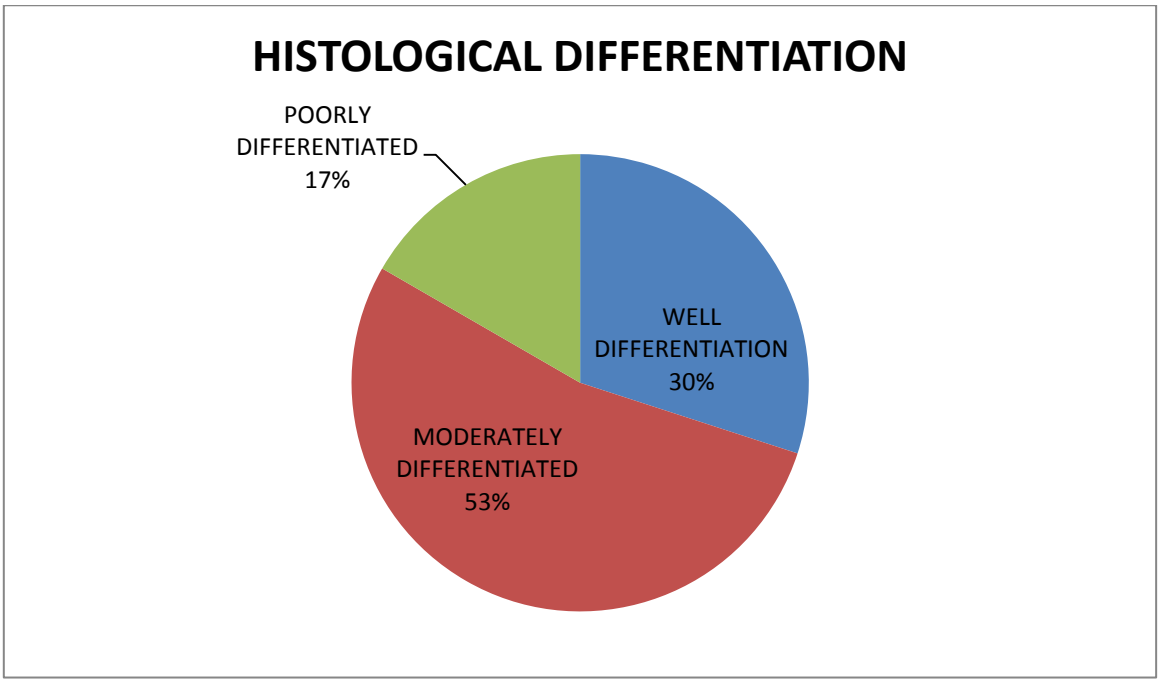


Figure: 31

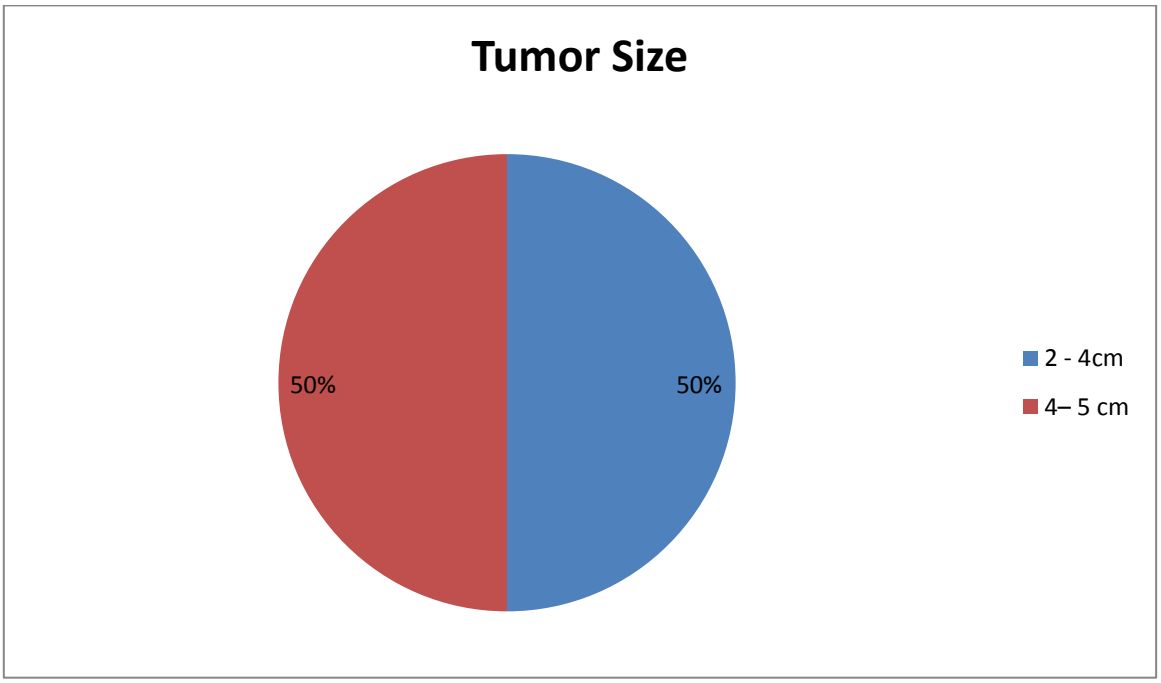


Figure: 32

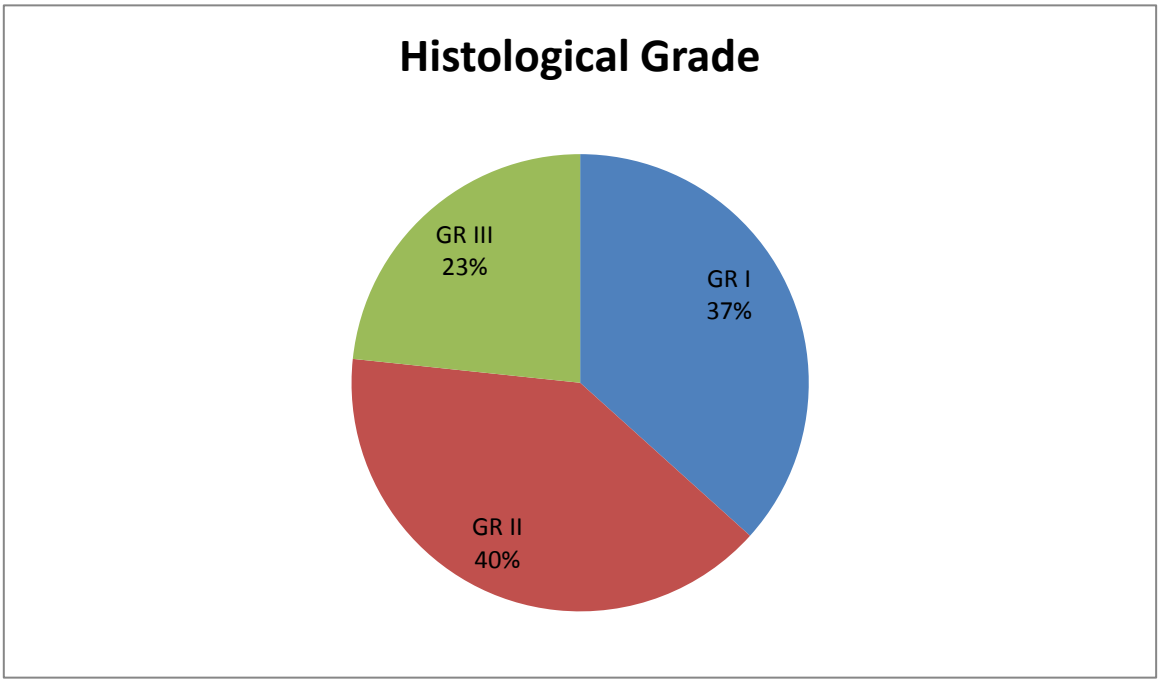


Figure: 33

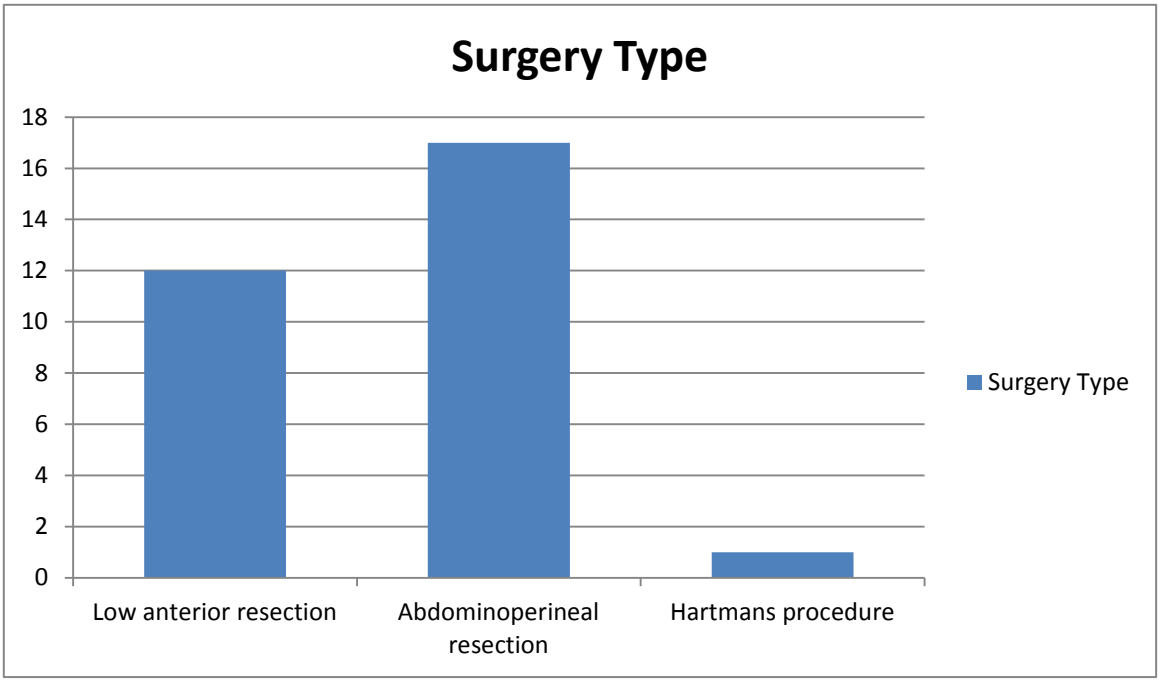


Figure: 34

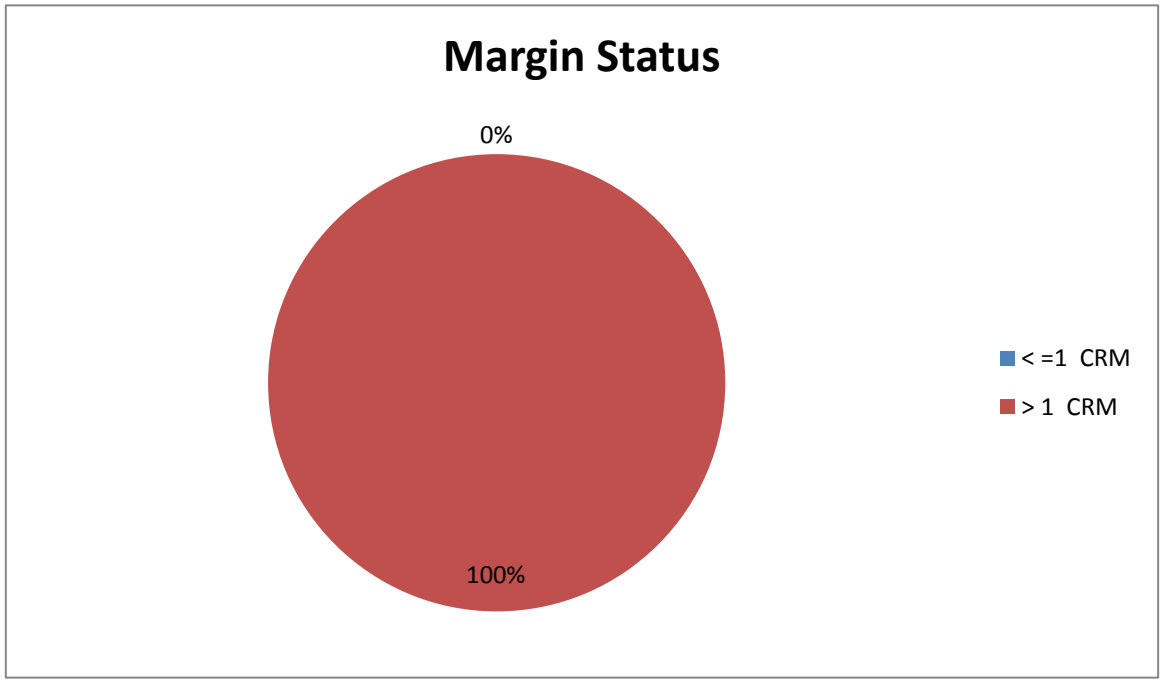


Figure: 35

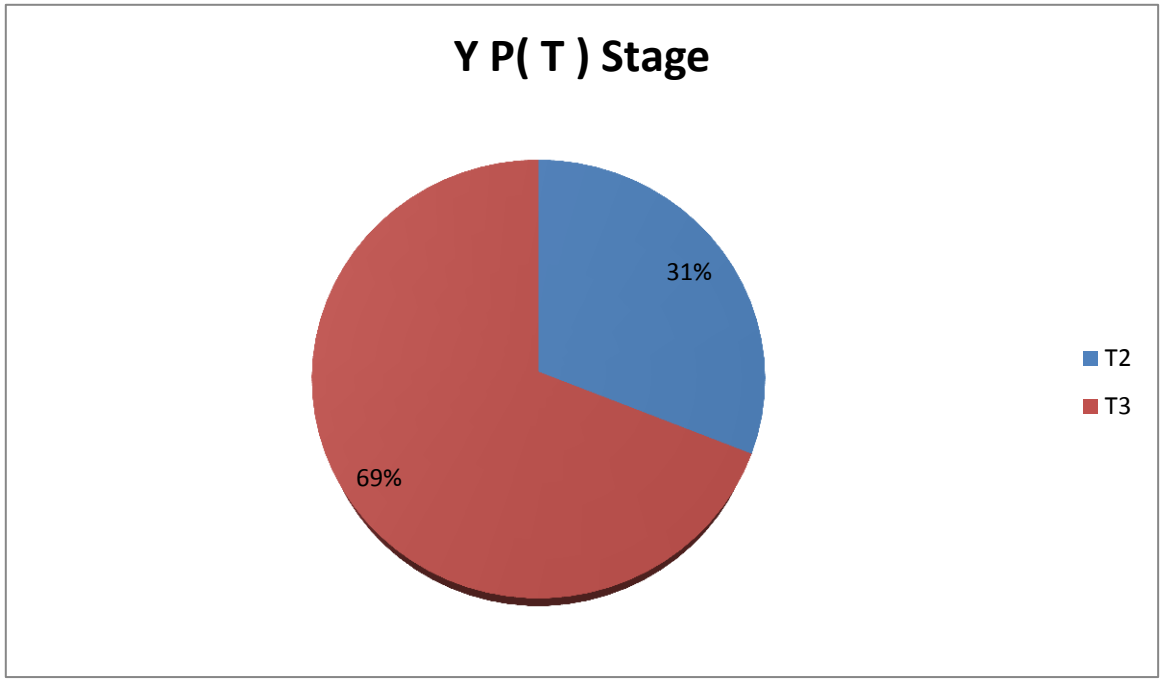


Figure: 36

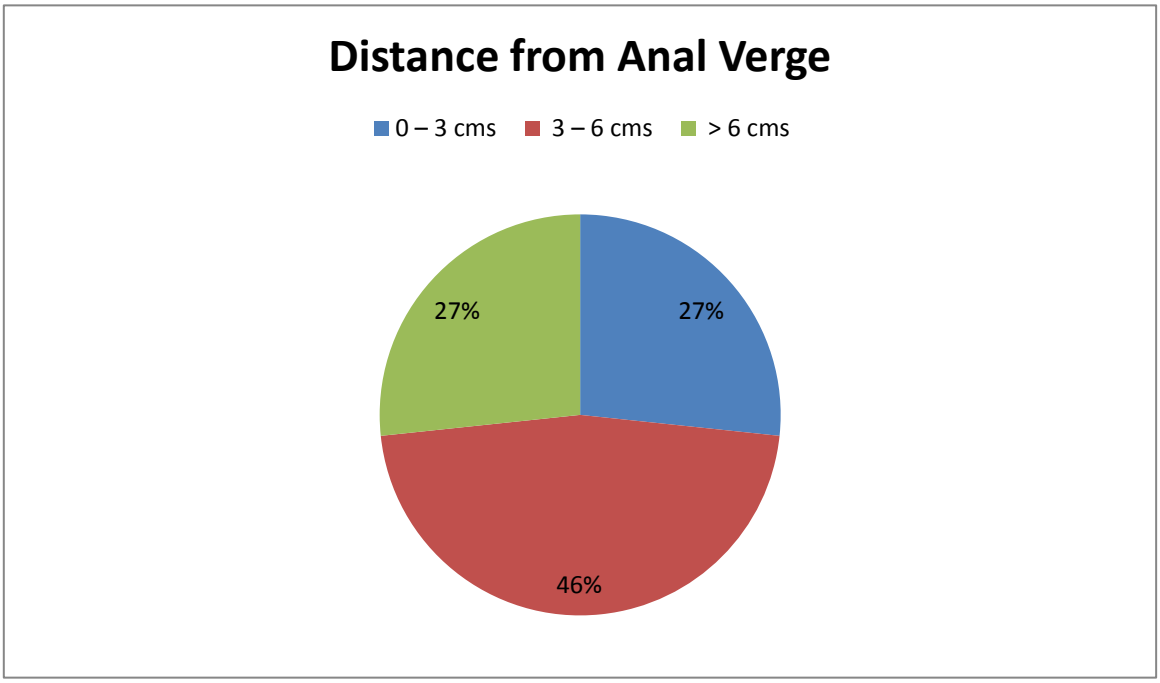


Figure: 37

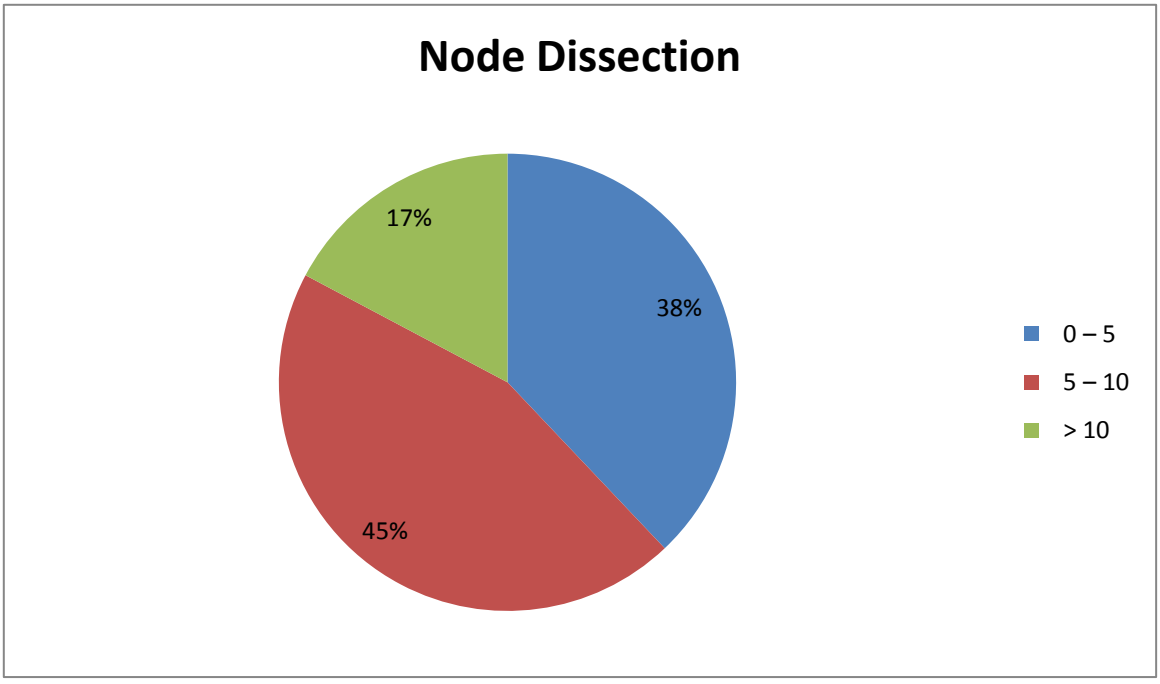


Figure: 38

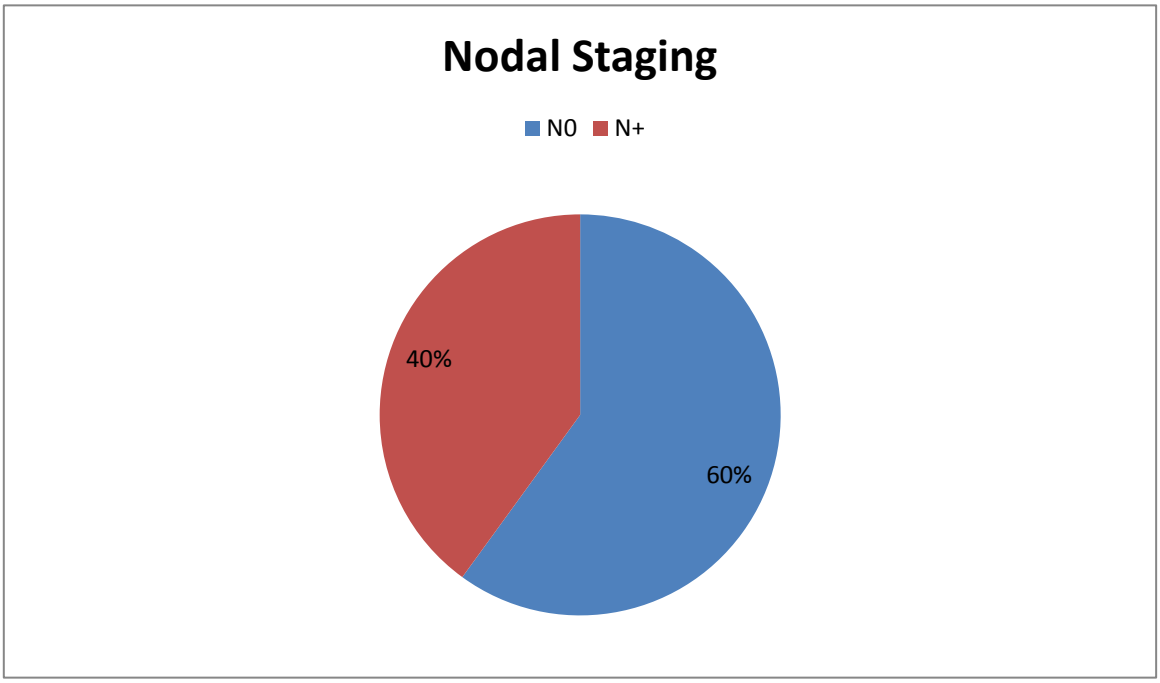
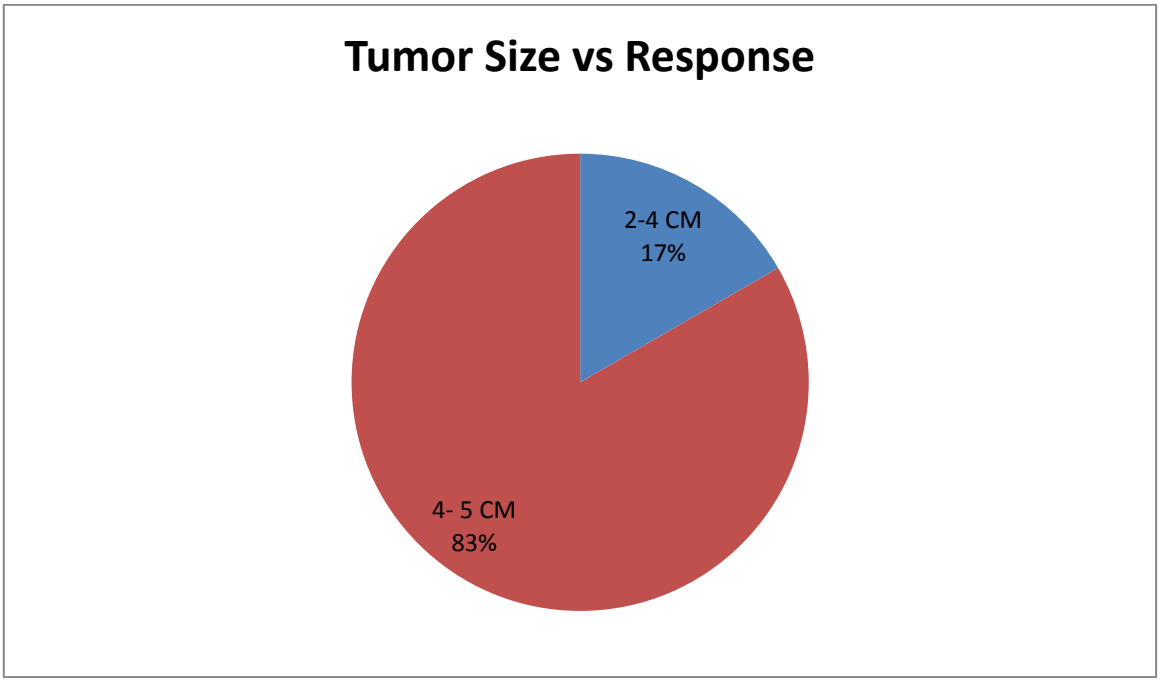


Figure: 39



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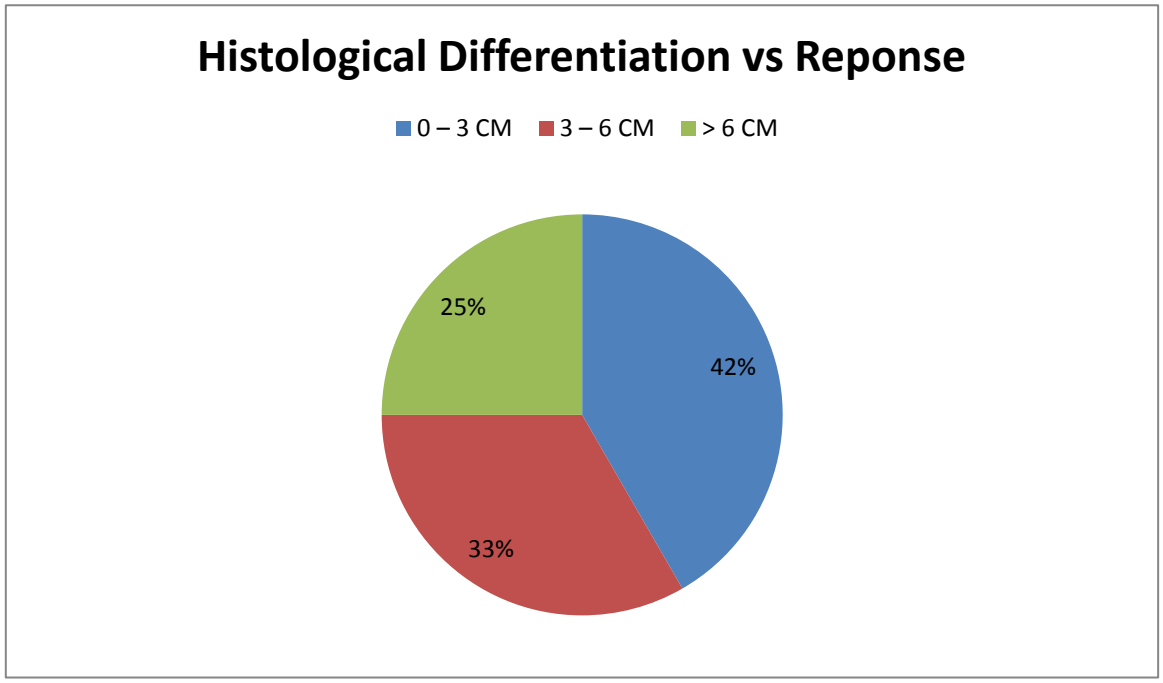


Figure: 41

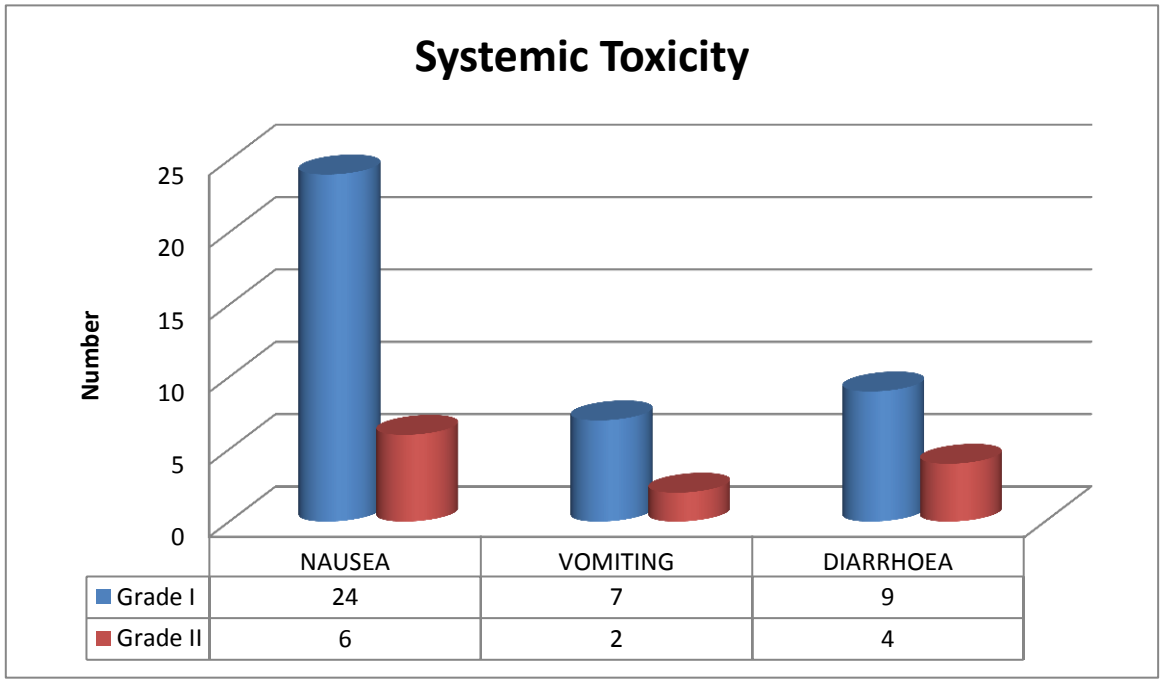


FIGURE : 17 TREATMENT PLANNING SYSTEM DATA

 THERAPLANPLUS External Beam Planning Version 3.7 05-Dec-2014 09:52:16

Plan Data - Rx: 480.0 cGy @ 90.00 % , Norm: 168.38

Beam	PA	LT LAT	RT LAT
Unit	PHOENIX-NEW	PHOENIX-NEW	PHOENIX-NEW
Rad.Type / Algorithm	Isotope / PB	Isotope / PB	Isotope / PB
Nom. Acc. Pot.(MV)	1.250	1.250	1.250
FSDD (cm)	80.00	80.00	80.00
Weight	1.000	1.000	1.000
Width (cm)	15.00	6.00	6.00
-x Jaw (cm)	-7.50	-3.00	-3.00
+x Jaw (cm)	7.50	3.00	3.00
Length (cm)	16.00	16.00	16.00
+y Jaw (cm)	8.00	8.00	8.00
-y Jaw (cm)	-8.00	-8.00	-8.00
X (cm)	-0.06	-13.57	12.99
Y (cm)	0.00	0.00	0.00
Z (cm)	-5.50	-0.37	-0.37
SSD (cm)	80.00	80.00	80.00
Depth (cm)	-0.00	0.00	0.00
Gantry (degrees)	0.0	270.0	90.0
Collimator (degrees)	0.0	0.0	0.0
Couch (degrees)	0.0	0.0	0.0
Surface	ON	ON	ON
Inhomogeneity	OFF	OFF	OFF
Bolus	N/A	N/A	N/A
Reference Width (cm)	15.09	6.04	6.04
Reference Length (cm)	16.10	16.10	16.10
Reference SSD (cm)	80.00	80.00	80.00
Reference Depth (cm)	0.50	0.50	0.50
Modifier	N/A	N/A	N/A
Compensator	N/A	N/A	N/A
Number of Fractions	0	0	0
CDR (cGy/MU or min)	88.650	88.650	88.650
Relative Dose Factor	1.052	0.980	0.980
ISF [(Fc / Fref)^2]	0.988	0.988	0.988
TAR (Rref*Fref/FSDD,dc)	1.071	1.052	1.052
1 / TAR (Rref*Fc/FSDD,dc)	0.934	0.951	0.951
TPR	1.000	1.000	1.000
TPRModCorrection	1.000	1.000	1.000
Mod. Output Factor	N/A	N/A	N/A
Mod.Tray Factor	N/A	N/A	N/A
Blk.Tray Factor	N/A	N/A	N/A
Cmp. Tray Factor	N/A	N/A	N/A
Decay To (mm/dd/yyyy)	05 Dec 2014	05 Dec 2014	05 Dec 2014
Decay Factor	0.638	0.638	0.638
User Defined Factor	1.000	1.000	1.000
Prescription Factor (cGy)	N/A	N/A	N/A
NDR (cGy/MU or min)	58.771	54.776	54.780
Shutter Correction (min)	0.000	0.000	0.000
MU or min / Fraction	N/A	N/A	N/A

Patient: Pereuma'ca rectum ID:2067-14
Anatomy: A
Plan : A
Modified: administrator 05-Dec-2014 09:43:59
Plan : C:\...\SAMPLE DATABASES\PLAN_S.MDB
UM : C:\...\SAMPLE DATABASES\UM_SAMPLE.MDB

FIGURE : 18 PLANNING WITHOUT WEDGES

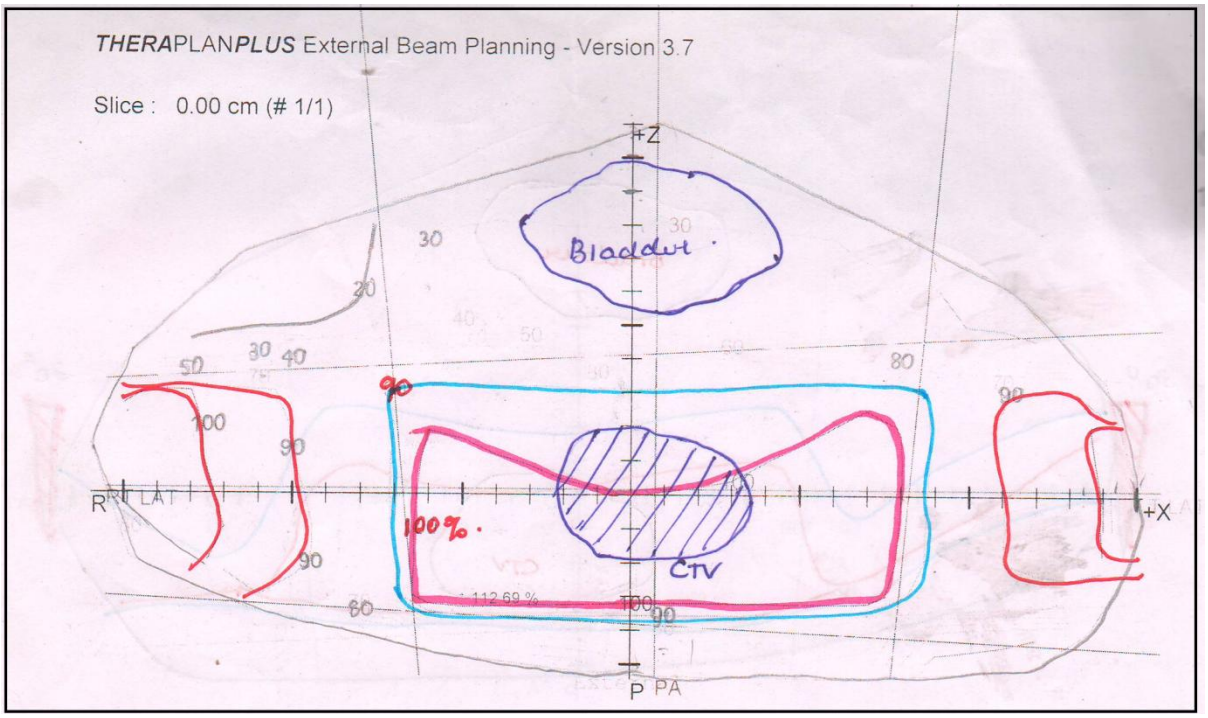
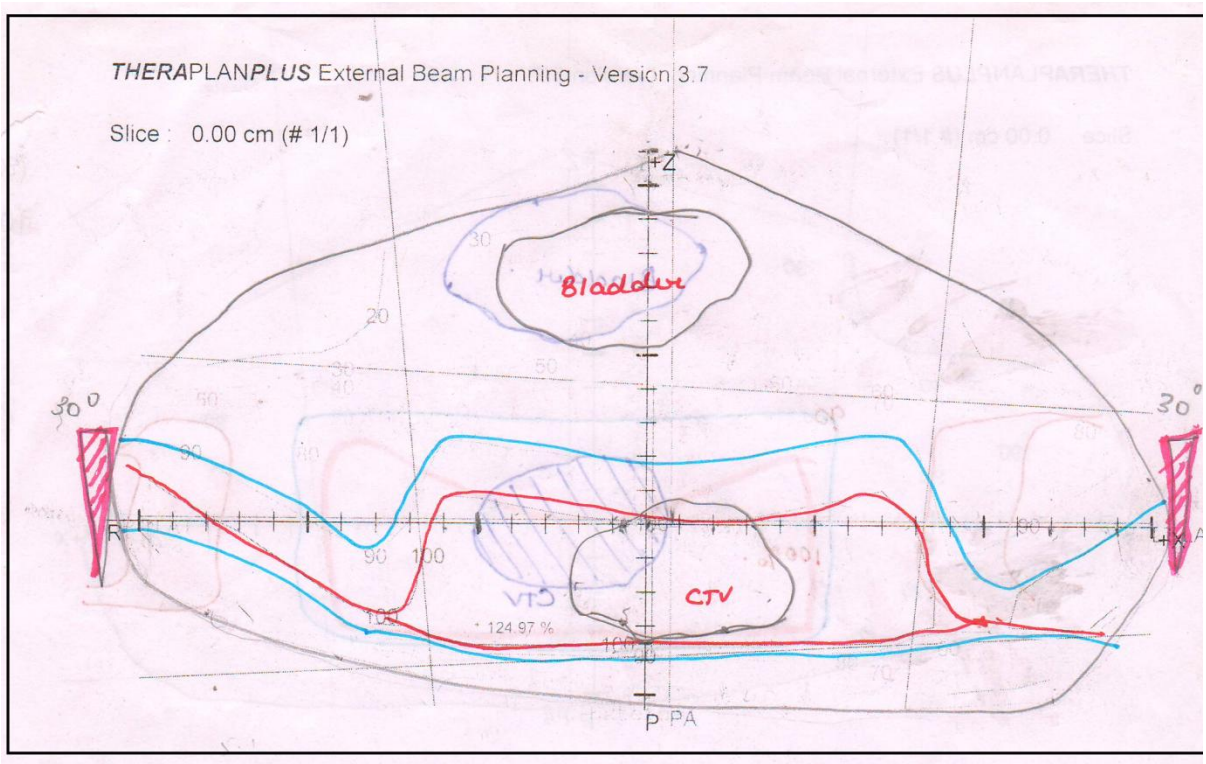


FIGURE : 19 PLANNING WITH WEDGES



DISCUSSION:

Although radiation has been associated with decreased rates of local recurrence in rectal cancers, it is also associated with increase in toxicity, compared to surgery alone. Hence patients with disease at the lower risk of local recurrence,,like small volume disease, T3 N0 M0 , proximal rectal tumors may be adequately treated with short course radiation.

The results of the present study show that neo adjuvant radiation in the form of short course therapy is feasible in our setup and should be considered in select cases of locally advanced rectal cancers. The study included a wide range of patients across the age groups between the eligibility ages of 18 years to 70 years. The study population was mostly males 16 patients with females 14 patients.

All the patients started on the protocol completed the course of radiation. But only 29 patients went in for curative resection which is TME .This one single patient had only a diversion procedure. It was because of adherence of tumor to adjacent structure. This implies indirectly that it is important to select cases carefully for this regimen.

The compliance of the patients to radiation was very good , since the radiation was only for 5 day. But few patients were reluctant to undergo permanent colostomy. So both the patients and the family members were to be counseled for it. Few patients were quite depressed following colostomy, they were given continuous support and rehabilitation during the further course of adjuvant treatment.

The patients should be counseled clearly before discharging from the hospital, the essential part of adjuvant chemo therapy and the right time patients had to return for the benefits of chemotherapy. Probably literacy will play a major role in this regard with literate people being able to grasp the consequences of defaulting adjuvant chemo therapy. Differentiation which is probably a surrogate for the mitotic rate of the tumor cells showed a significant correlation with response rates. Moderately differentiated tumors had a good response in terms of adequate reduction in tumor size as compared to other degrees of differentiation. It is a known fact that the T size of the primary tumor will have an impact on the immediate loco regional control as well as the recurrence free survival. The present study has confirmed the same fact with T size smaller tumors achieving more good responses.

In the present study too , tumors located more proximal to anal verge achieved adequate tumor regression , as evidenced by change in the T stage from T3 to T2. Polish randomisied trial and has shown that Long course is better to short course for more distally located tumors in terms of achieving adequate tumor downsizing and negative surgical margins.

So one must be precise in selecting cases for short course radiation. Patients must be selected on the basis of tumor T stage – T3, no nodal disease. The location of tumor from anal verge is also important in patient selection. More distal tumors should be treated with long course and proximally located tumors with short course. Preoperative assessment of tumor tethering and fixity should be considered for choosing between these two radiation regimens. Nodal status at the time of diagnosis plays a crucial role in deciding the treatment options. Nodal positivity warrants long course chemo radiation.

The **Swedish rectal cancer trial** demonstrated that short course preoperative radiation reduced the risk of local recurrence by half.

The **Dutch rectal cancer trial** showed that short course preoperative radiotherapy provides a definite benefit when it is combined with the best surgical approach – Total Mesorectal Exicision.

The **German rectal cancer trial** which compared pre operative with poat operative radiation, showed the superior benefit of pre operative regimen in terms of local control.

The trend is consistent with the common belief that long course is superior to short course , for a greater downsizing of the T stage, N status. However the **Polish trial** did not show any apparent effect on APR rates for rectal tumors.

In this meticulous study design, the value of short course radiation in selected patients is proved beyond doubt

STRENGTHS OF THE STUDY:

1. The study delivered the optimal neoadjuvant treatment in the form of short course radiation for selected patients.

2. The definitive part of the treatment, which is the surgery was done following the neoadjuvant phase.
3. The optimal adjuvant chemotherapy CAPEOX was delivered following surgery for a period of six months.
4. All the toxicities were graded using standard scale Common Toxicity Criteria for Adverse Events Version 4.
5. The response assessment was done using a standard scale .

LIMITATIONS OF THE STUDY:

1. Only neo adjuvant radiation was given without chemotherapy.
2. The radiation was delivered using 2D techniques. Delivering with 3D conformal techniques would have been the optimal technique.
3. There was no long term follow up of the patient which would have given the DFS and OS data for the sequential treatment.
4. The present study was a single arm study. A two arm comparative randomized study would have been better to settle the question of whether short course is better to long course chemo radiation.

CONCLUSION:

In locally advanced rectal cancers neo adjuvant treatment in the form of chemo radiation has now become the standard of care . It has shown to be the effective way in improving the local control rates and survival of patients. To prevent under treatment or over treatment of patients, accurate staging of the disease is mandatory for deciding the treatment policy, which varies with various stages of the disease. MRI has a major role to play in optimally staging the disease preoperatively.

Following rectal cancer surgery, irrespective of what the pathological response is adjuvant chemotherapy is indicated. Six months of peri operative chemotherapy is now the standard of care.

Both short course and long course pre operative regimens have been used in parallel for more than 15 years, in most European countries. In our country short course radiation is not widely practised. One reason for more lenient usage of long course is hypothetical belief that hypofractionated doses are associated with more late toxicities than long course conventional fractionation. Secondly for the fear that short course may not produce adequate tumor downsizing required. Encouragement

should be in favour of short course radiation in select patients as discussed upon, with lower risk of disease.

FUTURE DIRECTIONS:

Future directions would require modulating the various management strategies, using different drug combinations of chemotherapy with targeted agents, changing the sequence of treatment and using newer approaches to radiation therapy. The ultimate treatment goal is to achieve good response rates and survival. The greatest challenge will be to individualise care to improve long-term oncologic outcome, while minimizing the treatment related toxicities and maintaining good quality of life.

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Appendix I – Tables

1	TUMOR REGRESSION GRADING
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3	RT PORTAL MARGIN LATERAL PORTAL
4	BIOLOGICALLY EQUIVALENT DOSE
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6	GENDER DISTRIBUTION OF THE STUDY POPULATION
7	ECOG PERFORMANCE STATUS
8	SYMPTOMS/SIGNS
9	HISTOLOGICAL DIFFERENTIATION
10	SIZE OF TUMOR
11	HISTOLOGICAL GRADE
12	TYPE OF SURGERY
13	CIRCUMFERRENTIAL MARGIN STATUS
14	Y P(T) STAGE
15	DISTANCE FROM ANAL VERGE
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Annexure I

Information to Participants

Title: "NEOADJUVANT SHORT COURSE RADIOTHERAPY FOLLOWED BY SURGERY IN LOCALLY ADVANCED RECTAL CANCERS"

Principle Investigator: **Dr.Madhulika vijayakumar.**

Name of Participant:

Site: Department of Radiotherapy, Madras Medical College & RGGGH, Chennai-3

You are invited to take part in this research/ study/procedure. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries.

What is the purpose of this study?

The incidence of rectal cancers has been increasing worldwide due to economic development and industrialization. Surgery is the primary modality of treatment in spite of it, local and distant recurrence rates are high.pre operative treatment before surgery has shown significant reduction in the local recurrence and distal failure rates.pre operative treatment in the form of short course radiation for 5 days followed by surgery has shown promising results in tumor downstaging and good response rates. We want to assess the immediate loco regional response rates and treatment related toxicity.

We have obtained permission from the Institutional Ethics Committee.

The study design: Single arm Prospective study.

Study Procedures:

The study involves assessment of response and toxicity in locally advanced rectal cancers treated with short course pre operative radiotherapy

followed by surgery, which will need complete blood investigations, CT chest, MRI pelvis and assessment by surgeon &anaesthetist as a part of standard protocol for any other patients receiving radiotherapy. Following radiotherapy you will be undergoing surgery after 2 weeks .The tests are essential to monitor your condition, and to assess the safety and efficacy of treatment. You may have to come to the hospital for examination and investigations apart from your scheduled visits, if required.

Possible risks to you: None greater than standard patients receiving radiotherapy.

Possible benefits to you: Shorter treatment duration during time compared to patients treated with conventional fractions.

Possible benefits to other people: The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

Confidentiality of the information obtained from you:

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history).By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, Institutional Ethics Committee and any person or agency required by law like the Drug Controller General of India to view your data, if required. The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.

Signature of Investigator **Signature of Participant**

Date **Date**

Annexure II

INFORMED CONSENT FORM

TITLE OF THE STUDY**:** " **NEOADJUVANT SHORT COURSE RADIOTHERAPY FOLLOWED BY SURGERY IN LOCALLY ADVANCED RECTAL CANCERS.**

NAME OF THE PARTICIPANT:

NAME OF THE PRINCIPAL(Co – Investigator): DR.Madhulika Vijayakumar.

NAME OF THE INSTITUTION: MADRAS MEDICAL COLLEGE

I, _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in " **NEOADJUVANT SHORT COURSE RADIOTHERAPY FOLLOWED BY SURGERY IN LOCALLY ADVANCED RECTAL CANCERS** "

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments I am taking or have taken in the past 12 months including any native (alternative) treatment.
6. I have been advised about the risks associated with my participation in this study.*****
7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.*
8. I have not participated in any research study within the past 12month(s). *
9. I agree to undergo complete blood count, renal and liver function test, CT scan chest, MRI pelvis.
10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital. *
11. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent. *
12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
13. I have understand that my identity will be kept confidential if my data are publicly presented.
14. I have had my questions answered to my satisfaction.
15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____ Signature_____ Date_____

Name and Signature of impartial witness (required for illiterate patients):

Name _____ Signature_____ Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent

Name _____ Signature_____ Date_____

Annexure III

ஆய்வு தகவல் தாள்

ஆய்வு தலைப்பு:

மலக்குடல் புற்றுநோய்க்கு மாற்றுக்கதிர் இயக்க சிகிச்சையை தொடர்ந்த அறுவை சிகிச்சை மற்றும் புற்றுநோய் மருந்து மூலம் சிகிச்சை அளிப்பது தொடர்பான ஆய்வு.

ஆய்வாளர்:

பங்கேற்பாளர்:

இந்த ஆய்வு இராஜீவ் காந்தி அரசு பொது மருத்துவமனையில் நடைபெற உள்ளது. நீங்களும் இந்த ஆய்வில் பங்கேற்க நாங்கள் விரும்புகிறோம். இதிலுள்ள தகவலின் அடிப்படையில் இந்த ஆய்வில் பங்கேற்பதா அல்லது வேண்டாமா என்று நீங்கள் முடிவு செய்து கொள்ளலாம். உங்களது சந்தேகங்களை எங்களிடம் கேட்டு நிவர்த்தி செய்து கொள்ளலாம்.

ஆய்வின் நோக்கம்:

மாறிவரும் பொருளாதார காரணிகள் மற்றும் வாழ்க்கை முறையின் காரணமாக மலக்குடல் புற்றுநோயினால் பாதிக்கப்பட்டவர்களின் எண்ணிக்கை சமீபகாலங்களில் அதிகரித்து வருகிறது. பிரதானமாக இதற்கு அறுவை சிகிச்சை மூலம் சிகிச்சை அளிக்கப்பட்டாலும், புற்றுநோய் மீண்டும் வருவதற்கான வாய்ப்புகள் அதிகம். இந்நிலையில் அறுவை சிகிச்சைக்கு முன்கூட்டிய மாற்றுக்கதிர் வீச்சு சிகிச்சை இந்த வாய்ப்பினை கணிசமான அளவில் குறைக்கிறது. இந்த மாற்று கதிர்வீச்சு சிகிச்சை 5 நாட்களுக்கு அளிக்கப்பட்டு, இரண்டு வார

இடைவெளிக்குப் பின் அறுவை சிகிச்சை மேற்கொள்ளப்படும்போது நல்ல பலன் அளிப்பதாக தெரிகிறது. இந்த சிகிச்சை முறையின் பலன்களையும், பக்க விளைவுகளையும் அளவிட விரும்புகிறோம்.

இந்த ஆய்விற்கு மருத்துவமனையின் நெறிமுறைக் குழுவின் ஒப்புதல் பெற்றுள்ளோம்.

ஆய்வின் செயல்முறை:

இந்த ஆய்வுத் திட்டத்தின்படி, உங்களுக்கு மாற்று கதிர்வீச்சு சிகிச்சை 5 நாட்களுக்கு அளிக்கப்பட்டு, இரண்டு வார இடைவெளிக்குப் பின் அறுவை சிகிச்சை மேற்கொள்ளப்படும். இதற்காக இரத்தப் பரிசோதனை, சி.டி சோதனை உள்ளிட்ட, மாற்றுக்கதிர் வீச்சு சிகிச்சை பெறுபவர்களுக்கு மேற்கொள்ளப்படும் வழக்கமான பரிசோதனைகள் அனைத்தும் செய்யப்ப்படும். இந்த பரிசோதனைகள் உங்களது உடல் நலத்தையும், சிகிச்சையின் பலனையும் கண்டறிய முக்கியமானவையாகும். சில சமயங்களில் இந்த பரிசோதனைகளுக்காக நீங்கள் உங்களுக்கு அறிவிக்கப்பட்ட வருகை நாட்கள் தவிரவும் சில நாட்கள் மருத்துவமனை வர வேண்டியிருக்கலாம்.

ஆய்வினால் ஏற்படும் நன்மைகள்:

இந்த ஆய்வில் கலந்து கொள்வதன் மூலமாக நீங்கள் நோயின் தன்மையில் முன்னேற்றம் பெறலாம். மேலும் வருங்காலத்தில் பிற நோயாளிகளும் பயன் பெற இந்த ஆய்வு உதவியாக அமையும்.

மருத்துவ சிகிச்சையின் தகவல்கள் குறித்த விவரங்கள்:

உங்கள் மருத்துவ சிகிச்சை குறித்த தகவல்கள் இரகசியமாக பாதுகாக்கப்படும் (பெயர், மருத்துவ

பரிசோதனையின் முடிவு, மருத்துவ ஆய்வு முடிவு). இந்த தகவல் தாளில் கையெழுத்திடுவதன் மூலம் உங்களைப் பற்றிய குறிப்புகள் மற்றும் எடுத்துக் கொண்ட சிகிச்சை முறையைப் பற்றி ஆய்வாளர் மற்றும் மருத்துவமனையின் நெறிமுறைக் குழுவைச் சேர்ந்தவர்கள் தேவைப்பட்டால் அறிந்து கொள்ளலாம் என்று சம்மதிக்கிறீர்கள். முடிவுகளை அல்லது வெளியிடும்போதோ அல்லது ஆய்வின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதை தெரிவித்துக்கொள்கிறோம்.

இந்த ஆய்வில் பங்கேற்காவிட்டாலும் நீங்கள் வழக்கமான சிகிச்சையை தொடர்ந்து பெறலாம்.

இந்த ஆய்வில் பங்கேற்பது தங்களுடைய விருப்பத்தின்பேரில்தான் இருக்கிறது; மேலும் எந்நேரமும் இந்த ஆய்விலிருந்து தாங்கள் பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்பு சிகிச்சையின் முடிவுகளை ஆய்வின்போதோ அல்லது ஆய்வின் முடிவிலோ தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

ஆய்வாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி: தேதி:

Annexure IV

சுய ஒப்புதல் படிவம்

ஆய்வு தலைப்பு:

மலக்குடல் புற்றுநோய்க்கு மாற்றுக்கதிர் இயக்க சிகிச்சையை தொடர்ந்த அறுவை சிகிச்சை மற்றும் புற்றுநோய் மருந்து மூலம் சிகிச்சை அளிப்பது தொடர்பான ஆய்வு.

பெயர்: வயது: தேதி:

வெளிநோயாளி எண்:

_____ என்பவராகிய நான், இந்த ஆய்வின் விவரங்களும், அதன் நோக்கங்களும் பற்றி முழுமையாக அறிந்து கொண்டேன். எனது சந்தேகங்கள் அனைத்திற்கும் தகுந்த விளக்கம் அளிக்கப்பட்டது. இந்த ஆய்வில் பங்குகொள்ள முழு சுதந்திரத்துடன் மற்றும் சுயநினைவுடன் சம்மதிக்கிறேன்.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் நன்கு புரிந்துகொண்டு எனது சம்மதத்தைத் தெரிவிக்கிறேன். இந்த சுய ஒப்புதல் படிவத்தைப் பற்றி எனக்கு விளக்கப்பட்டது.

இந்த ஆய்வினைப் பற்றிய அனைத்துத் தகவல்களும் எனக்குத் தெரிவிக்கப்பட்டது. இந்த ஆய்வில் எனது உரிமை மற்றும் பங்கினை அறிந்து கொண்டேன்.

இந்த ஆய்வில் பிறரின் நிர்ப்பந்தமின்றி, என் சொந்த விருப்பத்தின்பேரில்தான் பங்கு பெறுகிறேன். நான் இந்த ஆராய்ச்சியிலிருந்து எந்நேரமும் பின்வாங்கலாம் என்பதையும்,

ANNEXURE V

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 011 25363970

CERTIFICATE OF APPROVAL

To
Dr. Madhulika Vijayakumar,
Postgraduate M.D.(Radio-Therapy),
Madras Medical College,
Chennai – 600 003.

Dear Dr. Madhulika Vijayakumar,

The Institutional Ethics Committee has considered your request and approved your study titled **"Neoadjuvant Short Course Radiotherapy followed by Surgery in locally advanced Rectal Cancers". No.26102014.**

The following members of Ethics Committee were present in the meeting held on 07.10.2014 conducted at Madras Medical College, Chennai-3.

1. Dr.C.Rajendran, M.D.,	: Chairperson
2. Dr.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.R.Nandhini, M.D., Inst.of Pharmacology, MMC	: Member
5. Dr.Raghumani, Director Incharge, Inst.of Surgery	: Member
6. Prof.K.Ramadevi, Director i/c, Inst.of Biochemistry, MMC	: Member
7. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
8. Prof.S.G.Sivachidambaram, M.D., Director i/c, Inst.of Internal Medicine, MMC	: Member
9. Thiru S.Rameshkumar, Administrative Officer	: Lay Person
10. Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
11. Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் புரிந்து கொண்டேன்.

இந்த ஆய்வில் கலந்து கொள்வதன் மூலம் என்னிடம் பெறப்படும் தகவலை ஆய்வாளர் மருத்துவமனை நெறிமுரைக்குழுவினரிடமோ, அரசு நிறுவனத்திடமோ தேவைப்பட்டால் பகிர்ந்து கொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வு முடிவுகள் வெளியிடப்படும்போது, எனது பெயரோ, அடையாளமோ வெளியிடப்படாது என அறிந்து கொண்டேன். இந்த ஆய்வின் விவரங்களைக்கொண்ட தகவல் தாளைப் பெற்றுக்கொண்டேன். இந்த ஆய்விற்காக தேவைப்படும் பரிசோதனைகளை செய்துகொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வில் பங்கேற்கும்போது ஏதேனும் சந்தேகம் ஏற்பட்டால், உடனே ஆய்வாளரை தொடர்பு கொள்ளவேண்டும் என்பதை அறிந்து கொண்டேன்.

இச்சுய ஒப்புதல் படிவத்தில் கையெழுத்திடுவதன் மூலம் இதிலுள்ள அனைத்து விஷயங்களும் எனக்குத் தெளிவாக விளக்கப்பட்டது என்று தெரிவிக்கிறேன் என்று புரிந்து கொண்டேன். இச்சுய ஒப்புதல் படிவத்தின் ஒரு நகல் எனக்கு கொடுக்கப்படும் என்று தெரிந்து கொண்டேன்.

ஆய்வாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி: தேதி: